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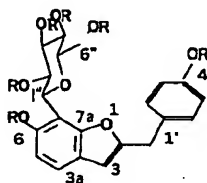
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(54) Title: NOVEL GLUCOPYRANOSIDE, PROCESS FOR ISOLATION THEREOF, PHARMACEUTICAL COMPOSITION CONTAINING SAME AND USE THEREOF



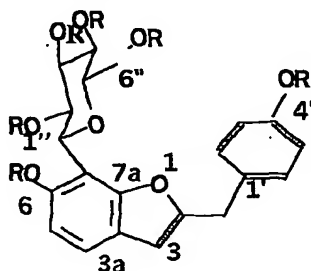
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(57) Abstract: A novel glucopyranoside, 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside of the formula (1) isolated from *Pterocarpus marsupium* and to a process for the isolation thereof is disclosed. The invention also relates to a pharmaceutical composition containing 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside and to method for the treatment of diabetes using said compound.

# NOVEL GLUCOPYRANOSIDE, PROCESS FOR ISOLATION THEREOF, PHARMACEUTICAL COMPOSITION CONTAINING SAME AND USE THEREOF

## Field of the invention

The present invention relates to a novel glucopyranoside, 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1



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The present invention also relates to a process for the isolation of said novel glucopyranoside of formula 1 from *Pterocarpus marsupium*.

More particularly, the present invention relates to a process of isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of formula 1, from *Pterocarpus marsupium*. The present invention also relates to a pharmaceutical composition containing 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1 and to method for the treatment of diabetes using said compound of formula 1.

## Background of the invention

*Pterocarpus marsupium* Roxb (*Leguminosae*) also known as Indian Kino tree or Bijasar, is common in the hilly regions of central and peninsular India [Jain, S. K., Medicinal Plants, National Book Trust, New Delhi, 1968, p. 116]. The extracts of leaves, flowers and gum of this tree have been used medicinally in the treatment of diarrhea, toothache, fever, urinary tract and skin infections. [Chopra, R. N., Chopra, I. C., Handa, K. L. and Kapur, L. D., Indigenous Drugs of India, 2nd Ed., Dhar, U. N. and Sons Private Limited, Calcutta, 1958, p. 522]. The extract of the bark has long been regarded as useful in the therapy of diabetes [Kirtikar, K. R. and Basu, B. D., Indian Medicinal Plants, 2nd Ed., edited by Blatter, E., Cailles, J. F. and Mhaskar, K. S., Singh and Singh, Delhi, India, 1975, p. 2135]. It is reported by Chakravathy et al [Chakravathy, B. K., Gupta, S. and Gode, K. D., *Lancet*, 1982, 272 (and references cited therein)] that the active hypoglycemic principle of the bark is (-)-epicatechin and that its effect is due to the regeneration of pancreatic beta cells. However,

this claim has been questioned by Kolb et al [Kolb, H., Kiesel, U., Grenlich, B. and Bosch, J. V. D., *Lancet*, 1982, 1303.] and Sheehan et al [Sheehan, E. W., Zemaitis, M. A., Slatkin, D. J. and Schiff, Jr., P. L., *Journal of Natural Products*, 1983, 46, 232]. It is now felt that further investigation is necessary before (-)-epicatechin can be considered a viable antidiabetic agent for use in human clinical studies.

Practitioners of the Indian System of Medicine are of the view that the heartwood rather than the bark of *Pterocarpus marsupium* is useful for treatment of diabetic patients and that older the plant more efficacious is its heartwood. It is also claimed that only heartwood that is distinctly red in colour and which imparts a red colouration with bluish green fluorescence to water in which it is kept soaked is suitable for use as an antidiabetic drug.

Hypoglycaemic effects of aqueous or alcoholic extracts of heartwood of *Pterocarpus marsupium* have been verified by experimental [Shah, D. S., *Indian Journal of Medical Research*, 1967, 55, 166 and references cited therein; Gupta, S. S., *Indian Journal of Medical Research*, 1963, 51, 716] and clinical studies [Sepha, G. C. and Bose, S. N., *J. Ind. Med. Assoc.*, 1956, 27, 383; Kedar, P. and Chakrabarti, C. H., *Maharashtra Med. J.*, 1981, 28, 165]. The heartwood of *Pterocarpus marsupium* is rich in phenolics. Chemical investigation on heartwood of *P. marsupium* dates back to 1946 but early works [Bhargava, P. N., *Proc. Ind. Acad. Sci.*, 1946, 24A, 496] on this drug are fragmentary in nature. Previous reported studies on this plant disclose the following chemical constituents.

1. The ether extract of *P. marsupium* heartwood furnished isoflavonoid glycol 4,4'-dihydroxy- $\alpha$ -methylhydrobenzoin designated Marsupol [Rao, A. V. S., Mathew, J., *Phytochemistry*, 1982, 21, 1837], a benzofurannone derivative, 2,4',6-trihydroxy-4-methoxybenzo(b)furan-3(2H)-one designated carpusin [Mathew, J. and Rao, A. V. S., *Phytochemistry*, 1983, 22, 794], 2-propanol derivative, 1,3-bis (4-hydroxyphenyl)propan-2-ol, designated propterol [Rao, A. V. S., Mathew, J. and Shankaran, A. V. B., *Phytochemistry*, 1984, 23, 897], 1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)propan-2-ol designated propterol B [Mathew, J., Rao, A. V. S. and Rambhav, S. *Current Science*, 1984, 53, 576], 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methyl benzyl) chroman-4-one [Jain, S. C., Sharma, S. K., Kumar, R., Rajwansh, V. K. and Babu, V. R., *Phytochemistry*, 1997, 44, 765].
2. Ethyl acetate soluble fraction of alcoholic extract of the heartwood furnished pterosupin  $\beta$ , 2', 4,4'-tetrahydroxy-3'(c- $\beta$ -D-glucopyranoside)dihydrochalcone [Adinarayana, D., Syamsundar, K. V., Seligmann, O., and wagner, H., (*Z.Naturforsch.*, 1982, 37C, 145)],

- Marsupinol [Trivedi, J. J., *Indian J. Phys. Pharmacol*, 1997, 15, 51], 5, 4'-dimethoxy-8-methylisoflavone-7-O- $\alpha$ -L-rhamnopyranoside, retusin-O- $\beta$ -D-glucopyranoside and irisolidine-7-O- $\alpha$ -L-rhamnopyranoside [Mitra, J. and Joshi, T., *Phytochemistry*, 1982, 21, 2429] and 5, 7'-dihydroxy-6-methoxy-7-O- $\alpha$ -L-rhamnopyranoside [Mitra, J. and Joshi, T., *Phytochemistry*, 1983, 22, 2326] obtained from the ethyl acetate soluble fraction of alcoholic extract of the heartwood.
3. Novel benzofuranone derivative, 2,6-dihydroxy-2-(*p*-hydroxybenzyl)-4-methoxy-3(2H)-benzofuranone designated marsupin [Maurya, R., Ray, A. B., Duah, F. K., Slatkin, D. J. and Schiff, P. L. Jr., *Heterocycles*, 1982, 19, 2103], pterostilbin, (2S)-hydroxyflavone, isoliquiritigenin, liquiritigenin, 7, 4'-dihydroxyflavone, 5-deoxykaempferol and 3,7,4'-trihydroxyflavone [Maurya, R., Ray, A. B., Duah, F. K., Slatkin, D. J. and Schiff, P. L. Jr., *J. Nat. Prod.* 1984, 47, 179], two C-glycosides, 8-C- $\beta$ -D-glucopyranosyl-3, 7, 4'-trihydroxy and 3, 7, 3', 4'-tetrahydroxy flavone and 3'-C- $\beta$ -D-glucopyranosyl- $\alpha$ -hydroxy dihydrochalcone [Bezuidenhout, B. C. B., Brandt, E. V., and Ferreira, E. V., *Phytochemistry*, 1987, 26, 531] from ethyl acetate extract of defatted heartwood.

However, the prior art does not provide any details about the biological activities associated with such chemical constituents. Also prior art discloses only preparation of ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract but does not disclose any method of preparing water extracts of heartwood of *Pterocarpus marsupium* and attempting to isolate any chemical constituents therefrom.

#### Objects of the invention

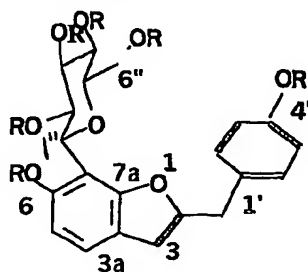
The main object of the invention is to accordingly prepare water extracts of the heartwood of *Pterocarpus marsupium* and to obtain chemical constituents therefrom.

It is another object of the invention to obtain novel bioactive fractions from water extracts of heartwood of *Pterocarpus marsupium* which are useful in treatment of diabetes.

#### Summary of the invention

The above and other objects of the invention are achieved by partitioning an aqueous extract of powdered heartwood of *Pterocarpus marsupium* with different organic solvents. The novel bioactive fraction, 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside is isolated from the polar fraction by chromatographic techniques and is found to show hypoglycaemic activity. There is no disclosure in the prior art of this compound since work had been done in the art on the ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract.

Accordingly, the present invention provides a novel glucopyranoside 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of formula 1 where R is H or COCH<sub>3</sub>



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The present invention also provides a process for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1 which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
- (b) extracting the powdered plant material with a protic solvent,
- (c) concentrating the extract to minimum volume and partitioning with different organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue.,
- (d) isolating 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside from the residue.

In one embodiment of the invention, the protic solvent used for preparing the extract in step (b) is selected from the group consisting of water, methanol, ethanol, propanol, butanol and any mixture thereof.

In another embodiment of the invention, the organic solvents used in step (c) comprise solvents of increasing polarity containing 1 to 6 carbon atoms in the molecule.

In another embodiment of the invention, the organic solvents of increasing polarity used in step (c) to remove the non-polar components comprise hexane, chloroform, methanol and ethanol in that order.

In another embodiment of the invention the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate and methanol in that order.

In another embodiment of the invention the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate, propanol and *n*-butanol in that order.

In another embodiment of the invention, the chromatographic methods used for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside is selected from MPLC, HPLC and flash chromatography.

The present invention also provides a pharmaceutical composition containing a  
5 pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of formula 1 in a pharmaceutically acceptable carrier.

In one embodiment of the invention, the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.

10 The invention also relates to a method for the treatment of diabetes comprising administering a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside to a patient.

In one embodiment of the invention, the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in said composition is in the range of  
15 0.5 mg to 15 mg per kg of body weight of the patient.

The present invention also relates to the use of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in the preparation of a pharmaceutical composition for the treatment of diabetes.

In one embodiment of the invention, the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in said composition is in the range of  
20 0.5 mg to 15 mg per kg of body weight of the patient.

#### Detailed description of the invention

The present invention provides a process for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside which comprises:

- 25 (a) powdering the heartwood of the plant *Pterocarpus marsupium*,  
(b) extracting the powdered plant material so prepared with a protic solvent,  
(c) concentrating the aqueous extract to minimum volume and partitioning with organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue;  
30 (d) isolating the 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside from residue.

The solvent used for preparing the extract may be water, methanol, ethanol, propanol and butanol and like or their mixtures. The organic solvent used in step (c) to remove the

non-polar components is selected from hexane, ethyl acetate, methanol, ethanol, propanol, n-butanol and chloroform. The polar solvent used to extract the aqueous layer is selected from ethyl acetate, propanol, butanol and a mixture thereof. The chromatographic methods used for the isolation of methanol, ethanol, propanol may be MPLC, flash chromatography etc.

5 In the MPLC method the required eluting solvent is pumped through the column and in the flash chromatography solvent is pushed with air pressure. The compound of the invention was recrystallised from a mixture of ethyl acetate and methanol, mp 117 - 118°C,  $[\alpha]_D^{19} + 9.15^\circ$  (MeOH, c, 0.295), showed UV maxima at 242, 253 and 284 nm in methanol. The molecular formula of the compound was established as  $C_{21}H_{22}O_8$  on the basis of strong  
10 peak at m/z 402  $[M]^+$  in the FAB mass spectrum, together with the support of spectroscopic methods.

The compound 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside was isolated from the n-butanol soluble fraction of the water decoction of the heartwood of *P. marsupium* which has shown antidiabetic activity in both humans and animals. There is no  
15 disclosure in the prior art of this compound since work had been done in the art on the ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract.

The process of isolating active principle from *Pterocarpus marsupium* comprises partition of the aqueous extract of powdered heartwood with different organic solvents containing 1-6 carbon atoms in the molecule. 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-  
20 C-β-D-glucopyranoside of formula 1 is isolated from polar fraction by applying modern chromatographic techniques such as medium pressure liquid chromatography (MPLC), high pressure liquid chromatography (HPLC) and flash chromatography using silica gel (230 - 400 mesh) and shows hypoglycaemic activity.

The 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside isolated  
25 from *Pterocarpus marsupium* possesses anti-diabetic activity.

The chromatographic methods used for the isolation of 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside may be MPLC, flash chromatography etc. In the MPLC method the solvent is pumped through the column and in the flash chromatography is pushed with air pressure. The IR spectrum revealed absorptions at 3300  
30 for hydroxyls, 1600, 1584, 1512  $cm^{-1}$  for aromatic ring. The  $^1H$  and  $^{13}C$  NMR spectra exhibited two sets of multiplets for aromatic protons centered at  $\delta$  7.18 (H-5,3',5') and 6.70 (H-4, 2', 6'), one furan proton singled at  $\delta$  6.27 (H-3),  $\delta C$  102.9, a singlet for one benzylic methylene group at  $\delta$  3.65,  $\delta C$  34.2 and multiplet at  $\delta$  3.00 - 5.00 for sugar protons. The

spectral data suggest that the compound of the invention is a benzofuran C-glucoside containing one phenolic hydroxy group in ring -C. On acetylation the compound of the invention furnished hexa-acetate where in formula 1 R is acetyl, recrystallised from methanol, mp 80-81°C,  $[\alpha]_D^{19} -85.40^\circ$  (CHCl<sub>3</sub>, c, 0.185), showed UV maxima at 248, 252, 278, 286 nm in chloroform, IR in KBr 1725, 1600, 1580, 1385 cm<sup>-1</sup>, the molecular formula of the hexaacetate being C<sub>33</sub>H<sub>34</sub>O<sub>14</sub>, m/z 655[M+1]<sup>+</sup>. The <sup>1</sup>H and <sup>13</sup>C NMR spectra indicated the presence of four singlets for sugar acetate groups at  $\delta$  2.17, 2.16, 2.09, and 2.08, two singlets for aromatic acetate groups at  $\delta$  2.42, and 2.35, one singlet for benzylic methylene group at  $\delta$  4.16,  $\delta$ C 34.3, one singlet for furan proton at  $\delta$  6.38,  $\delta$ C 103.4, two *ortho* coupled aromatic protons at  $\delta$  7.46 (1H, d, J = 8.4 Hz), and 6.92 (1H, d, J = 8.4 Hz), one A<sub>2</sub>B<sub>2</sub> aromatic system at  $\delta$  7.36 (2H, d, J = 8.3 Hz) and 7.10 (2H, d, J = 8.3 Hz). The anomeric proton of sugar appeared at  $\delta$  5.02 (1H, d, J = 9.9 Hz),  $\delta$ C 74.5, indicating it to have the  $\beta$ -configuration on the basis of chemical shift and coupling constant [Roberts J.D., Weigert, F.J., Kroschwitz, J.I. and Reich, H.J., *J. Am. Chem.Soc.*, 1970, 92, 1338]. Further methine protons of sugar appeared at  $\delta$  5.73 (1H, d, J = 9.3 Hz), 5.42 (1H, d, J = 9.2 Hz) and 5.28 (1H, d, J = 9.4 Hz). Coupling constants for the methine protons H-1" to H-5" of the hexose showed an all *trans*-axial relationship and together with the methylene (H-6") resonances confirmed the identity of sugar as  $\beta$ -D-glucose. Further the carbon chemical shifts of the glucose moiety were congruent with those of C- $\beta$ -D-glucopyranosyl residue [Ikeya, Y., Sugama, K., and Maruno, M., *Chemistry and Pharmacology Bulletin*, 1994, 42, 2305] and HMBC spectra indicated it is linked to aglycone at C-7. On the basis of the above spectral data the structure of the compound was established as 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1 where R is hydrogen.

The compound was evaluated for hypoglycaemic activity in 18 hour fasted Wistar rats. In a dose of 15 mg/kg p.o., hypoglycaemic effect was recorded in all the treated rats. The mean fall recorded was 24 mg/100 ml blood, from an initial mean of 91 to mean of 67 mg/100 ml blood. As compared to this, conventional hypoglycaemic agents such as chlorpropamide used as a positive control showed mean fall of 18 mg/100 ml of blood.

The invention is described in detail by the examples given below which should not be construed to the limit of scope of the present invention.

#### Example 1

The powdered heartwood of *Pterocarpus marsupium* (1kg) was percolated with 80% aqueous ethanol (3x3 lits.) for a period of 48 hours. The resultant concentrate was partitioned



with hexane, chloroform, propanol and butanol in that order. The polar extract was subjected to MPLC using silica gel (100 - 200 mesh) for gross fractions with hexane, chloroform, methanol, ethanol in that order. The active compound was purified by repeated MPLC and flash chromatography over silica gel (230 - 400 mesh) using  $\text{CHCl}_3$  - MeOH (9:1) as solvent, to furnish 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1, (yield 0.031 - 0.041%), mp. 117 -118°C,  $[\alpha]_D^{19} + 9.15^\circ$  (MeOH, c, 0.295), and hexaacetate of compound of formula 1 where R is acetyl recrystallised from methanol, mp 80-81°C,  $[\alpha]_D^{19} -85.40^\circ$  ( $\text{CHCl}_3$ , c, 0.185).

#### Example 2

The heartwood of *Pterocarpus marsupium* was extracted with hot water for a period of 4 hours. The resultant concentrate was partitioned between hexane, chloroform, propanol and butanol in that order. The polar extract so obtained was subjected to flash chromatography employing silica gel (100 - 200 mesh) using hexane, chloroform, ethylacetate and methanol as solvent system to afford 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside rich fraction, which on repeated chromatography over silica gel (230 - 400 mesh) using EtOAc - MeOH (19:1) as solvent, furnished 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1, (yield 0.032 - 0.043%), mp. 117 -118°C,  $[\alpha]_D^{19} + 9.15^\circ$  (MeOH, c, 0.295), and hexaacetate of compound of formula 1 where R is acetyl recrystallised from methanol, mp 80-81°C,  $[\alpha]_D^{19} -85.40^\circ$  ( $\text{CHCl}_3$ , c, 0.185).

#### Example 3

The heartwood of *Pterocarpus marsupium* was boiled with water (16 times) till 1/4 volume of water is left, filtered, concentrated and partitioned between hexane, chloroform, ethyl acetate, propanol and n-butanol in that order. The polar extract obtained was subjected to column chromatography employing silica gel (60-120 mesh) using hexane, chloroform, ethyl acetate and methanol as solvent system to afford 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside rich fraction. The 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside rich fraction on repeated column chromatography over silica gel (100-200 mesh) using mixture of ethyl acetate - acetone (7:3), furnished 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1 (yield 0.031 - 0.044%), mp. 117 -118°C,  $[\alpha]_D^{19} + 9.15^\circ$  (MeOH, c, 0.295), hexaacetate of compound of formula 1 where R is acetyl, recrystallised from methanol, mp 80-81°C,  $[\alpha]_D^{19} -85.40^\circ$  ( $\text{CHCl}_3$ , c, 0.185).

**Advantages:**

1. The compound obtained 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside is a novel molecule with antidiabetic activity.
2. The method of isolation of 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside is comparatively simple.

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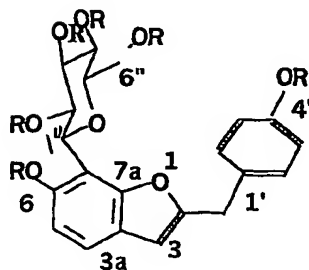
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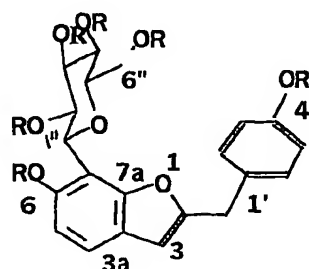
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We claim:

1. A novel glucopyranoside 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1



2. Process for the isolation of 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of the formula 1



which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
  - (b) extracting the powdered plant material with a protic solvent,
  - (c) concentrating the extract to minimum volume and partitioning with different organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue.,
  - (d) isolating the 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside from the residue.
3. Process as claimed in claim 2 wherein the protic solvent used for preparing the extract in step (b) is selected from the group consisting of water, methanol, ethanol, propanol, butanol and any mixture thereof.
  4. Process as claimed in claim 2 wherein the organic solvents used in step (c) comprise solvents of increasing polarity containing 1 to 6 carbon atoms in the molecule.

5. Process as claimed in claim 2 wherein the organic solvents of increasing polarity used in step (c) to remove the non-polar components comprise hexane, chloroform, methanol and ethanol in that order.
6. Process as claimed in claim 2 wherein the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate and methanol in that order.
7. Process as claimed in claim 2 wherein the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate, propanol and n-butanol in that order.
8. Process as claimed in claim 2 wherein the chromatographic methods used for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside is selected from MPLC, HPLC and flash chromatography.
9. The present invention also provides a pharmaceutical composition containing a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside of formula 1 in a pharmaceutically acceptable carrier.
10. Composition as claimed in claim 9 wherein the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.
11. Method for the treatment of diabetes comprising administering a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside to a patient.
12. Method as claimed in claim 11 wherein amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.
13. Use of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in the preparation of a pharmaceutical composition for the treatment of diabetes.
14. Use as claimed in claim 13 wherein the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- $\beta$ -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IN 02/00105

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D407/04 C07H7/06

A61K31/351 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 359 554 A (KOTOBUKI PHARMACEUTICAL COMPAN) 29 August 2001 (2001-08-29) abstract	1,11
A	BEZUIDENHOUDT B C B ET AL: "FLAVONOID ANALOGUES FROM PTEROCARPUS SPECIES" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 26, no. 2, 1987, pages 531-535, XP008005725 ISSN: 0031-9422 cited in the application page 532	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

29 January 2003

Date of mailing of the international search report

06/02/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
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Fax (+31-70) 340-3018

Authorized officer

de Nooy, A

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 02/00105

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 11,12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 02/00105

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB 2359554	A	29-08-2001	JP	2001288178 A	16-10-2001
			US	2001041674 A1	15-11-2001

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For two-letter codes and other abbreviations, refer to the "Guid-  
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ning of each regular issue of the PCT Gazette.

WO 2005/012318 A2

(54) Title: SUBSTITUTED FUSED HETEROCYCLIC C-GLYCOSIDES

(57) Abstract: This invention relates to substituted fused heterocyclic C-glycosides, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of diabetes and Syndrome X.



**SUBSTITUTED FUSED HETEROCYCLIC C-GLYCOSIDES**  
**FIELD OF THE INVENTION**

5 This invention relates to substituted fused heterocyclic C-glycosides, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of diabetes and Syndrome X.

**BACKGROUND OF THE INVENTION**

10 Diabetes is a chronic disorder affecting carbohydrate, fat and protein metabolism in animals.

Type I diabetes mellitus, which comprises approximately 10% of all diabetes cases, was previously referred to as insulin-dependent diabetes mellitus ("IDDM") or juvenile-onset diabetes. This disease is characterized by a progressive loss of insulin secretory function by beta cells of the pancreas. This characteristic is also shared by non-idiopathic, or "secondary", diabetes having its origins in pancreatic disease. Type I diabetes mellitus is associated with the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia; polyuria; polydipsia and/or hyperphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension which can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

25 Type II diabetes mellitus (non-insulin-dependent diabetes mellitus or NIDDM) is a metabolic disorder involving the dysregulation of glucose metabolism and impaired insulin sensitivity. Type II diabetes mellitus usually develops in adulthood and is associated with the body's inability to utilize or make sufficient insulin. In addition to the insulin resistance observed in the target tissues, patients suffering from type II diabetes mellitus have a relative insulin deficiency -- that is, patients have lower than predicted insulin levels for a given plasma glucose concentration. Type II diabetes mellitus is

characterized by the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia; polyuria; polydipsia and/or hyperphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension which can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

Syndrome X, also termed Insulin Resistance Syndrome (IRS), Metabolic Syndrome, or Metabolic Syndrome X, is recognized in some 2% of diagnostic coronary catheterizations. Often disabling, it presents symptoms or risk factors for the development of Type II diabetes mellitus and cardiovascular disease, including impaired glucose tolerance (IGT), impaired fasting glucose (IFG), hyperinsulinemia, insulin resistance, dyslipidemia (e.g., high triglycerides, low HDL), hypertension and obesity.

Therapy for IDDM patients has consistently focused on administration of exogenous insulin, which may be derived from various sources (e.g., human, bovine, porcine insulin). The use of heterologous species material gives rise to formation of anti-insulin antibodies which have activity-limiting effects and result in progressive requirements for larger doses in order to achieve desired hypoglycemic effects.

Typical treatment of Type II diabetes mellitus focuses on maintaining the blood glucose level as near to normal as possible with lifestyle modification relating to diet and exercise, and when necessary, the treatment with anti-diabetic agents, insulin or a combination thereof. NIDDM that cannot be controlled by dietary management is treated with oral antidiabetic agents.

Although insulin resistance is not always treated in all Syndrome X patients, those who exhibit a prediabetic state (e.g., IGT, IFG), where fasting glucose levels may be higher than normal but not at the diabetes diagnostic criterion, is treated in some countries (e.g., Germany) with metformin to prevent diabetes. The anti-diabetic agents may be combined with

pharmacological agents for the treatment of the concomitant co-morbidities (e.g., antihypertensives for hypertension, hypolipidemic agents for lipidemia).

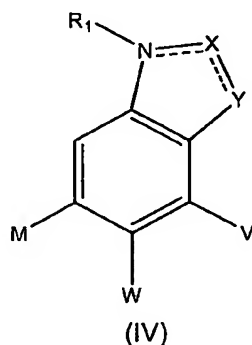
First-line therapies typically include metformin and sulfonylureas as well  
5 as thiazolidinediones. Metformin monotherapy is a first line choice, particularly for treating type II diabetic patients who are also obese and/or dyslipidemic. Lack of an appropriate response to metformin is often followed by treatment with metformin in combination with sulfonylureas, thiazolidinediones, or insulin. Sulfonylurea monotherapy (including all generations of drugs) is also a  
10 common first line treatment option. Another first line therapy choice may be thiazolidinediones. Alpha glucosidase inhibitors are also used as first and second line therapies. Patients who do not respond appropriately to oral anti-diabetic monotherapy, are given combinations of the above-mentioned agents. When glycemic control cannot be maintained with oral antidiabetics alone,  
15 insulin therapy is used either as a monotherapy, or in combination with oral antidiabetic agents.

One recent development in treating hyperglycemia is focused on excretion of excessive glucose directly into urine. Specific inhibitors of SGLTs  
20 have been shown to increase the excretion of glucose in urine and lower blood glucose levels in rodent models of IDDM and NIDDM.

SUMMARY OF THE INVENTION

One aspect of the present invention is directed to methods and compositions for the treatment or prophylaxis of diabetes, Syndrome X, or associated symptoms or complications. More specifically, this invention is directed to a novel method of treating diabetes or Syndrome X, or associated symptoms or complications thereof, in a subject afflicted with such a condition, said method comprising administering one or more glucose reabsorption inhibitors and administering one or more antidiabetic agent(s) for the treatment of diabetes or Syndrome X, or associated symptoms or complications thereof.

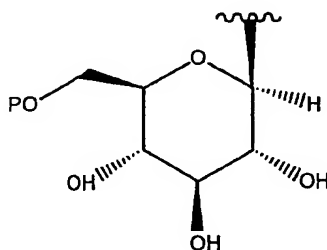
Another aspect of the invention features compounds of formula (IV)



wherein:

one of the dashed lines between  $NR_1$  and X or between X and Y is present, or both are absent;

two of V, M, and W are H and the third is



$R_1$  is H, or C<sub>1-4</sub> alkyl; or  $R_1$  is absent where the dashed line between  $NR^1$  and X is present,

X is N, C=O, CH, or C-Q-Z;

5

Y is N-Q-Z or C-Q-Z, where X is N, C=O, or CH;

Y is CH, where X is C-Q-Z;

Q =  $-(CH_2)_n-$  where n = 1 or 2;

10

Z is substituted or unsubstituted, and is selected from C<sub>3-7</sub> cycloalkyl, phenyl, a 5- or 6- membered heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, a biaryl, a 9- or 10-membered fused bicycyl (such as naphthyl), and a fused heterobicycyl, wherein said fused heterobicycyl has  
15 between 1 and 4 heteroatoms (and preferably between 1 and 3 or between 1 and 2 heteroatoms) independently selected from N, O, and S;

P = H, C<sub>1-7</sub> acyl, or (C<sub>1-6</sub> alkoxy)carbonyl;

20 or a pharmaceutically acceptable salt, thereof.

One aspect of the invention features a pharmaceutical composition comprising a glucose reabsorption inhibitor, at least one additional antidiabetic agent, and a pharmaceutically acceptable carrier. The invention also provides  
25 a process for formulating a pharmaceutical composition, comprising formulating together a glucose reabsorption inhibitor, one or more antidiabetic agent(s), and a pharmaceutically acceptable carrier.

An embodiment of the invention is a method for treating diabetes or  
30 Syndrome X, or associated symptoms or complications thereof in a subject, said method comprising administering to said subject a jointly effective amount of a glucose reabsorption inhibitor and administering to said subject a jointly

effective amount of at least one antidiabetic agent, said combined administration providing the desired therapeutic effect.

Another embodiment of the invention is a method for inhibiting the onset  
5 of diabetes or Syndrome X, or associated symptoms or complications thereof  
in a subject, said method comprising administering to said subject a jointly  
effective dose of a glucose reabsorption inhibitor and administering to said  
subject a jointly effective amount of one or more anti-diabetic agent(s), said  
combined administration providing the desired prophylactic effect.

10

In the disclosed methods, the diabetes or Syndrome X, or associated  
symptoms or complications thereof, is selected from IDDM, NIDDM, IGT, IFG,  
obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic  
ovarian syndrome, hypertension, ischemia, stroke, heart disease, irritable  
15 bowel disorder, inflammation, and cataracts.

Also included in the invention is the use of one or more glucose  
reabsorption inhibitors in combination with one or more antidiabetic agents for  
the preparation of a medicament for treating a condition selected from IDDM,  
20 NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy,  
atherosclerosis, polycystic ovarian syndrome or polycystic ovarian syndrome,  
hypertension, ischemia, stroke, heart disease, irritable bowel disorder,  
inflammation, and cataracts.

### DETAILED DESCRIPTION OF THE INVENTION

All diabetics, regardless of their genetic and environmental  
5 backgrounds, have in common an apparent lack of insulin or inadequate insulin  
function. Because transfer of glucose from the blood into muscle and fatty  
tissue is insulin dependent, diabetics lack the ability to utilize glucose  
adequately, which leads to undesired accumulation of glucose in the blood  
(hyperglycemia). Chronic hyperglycemia leads to decrease in insulin secretion  
10 and contributes to increased insulin resistance, and as a result, the blood  
glucose concentration is increased so that diabetes is self-exacerbated  
(Diabetologia, 1985, "Hyperglycaemia as an inducer as well as a consequence  
of impaired isle cell function and insulin resistance: implications for the  
management of diabetes", Vol. 28, p. 119); Diabetes Care, 1990, Vol. 13, No.  
15 6, "Glucose Toxicity", pp. 610-630). Therefore, by treating hyperglycemia, the  
aforementioned self-exacerbating cycle is interrupted so that the prophylaxis or  
treatment of diabetes is made possible.

US Patent NO. 6,153,632 to R. Rieveley discloses a method and  
20 composition stated to be for the treatment of diabetes mellitus (Type I,  
Impaired Glucose Tolerance ["IGT"] and Type II), which incorporates a  
therapeutic amount of one or more insulin sensitizers along with one or more of  
an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an  
alpha-glucosidase inhibitor for the treatment of diabetes mellitus.

25

According to one aspect, the invention features the combination of a  
PPAR modulator, preferably a PPAR  $\delta$  agonist, and an SGLT inhibitor,  
preferably an SGLT 2 inhibitor or a selective SGLT 2 inhibitor.

## A. Terms

Some terms are defined below and by their usage throughout this  
5 disclosure.



Unless otherwise noted, "alkyl" and "alkoxy" as used herein, whether used alone or as part of a substituent group, include straight, cyclic, and branched-chain alkyl having 1 to 8 carbon atoms, or any number within this  
10 range. For example, alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, 2-butenyl, 2-butyne, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. The alkyl and alkoxy group  
15 may be independently substituted with one to five, preferably one to three groups selected from halogen (F, Cl, Br, I), oxo, OH, amino, carboxyl, and alkoxy. The alkyl and alkoxy group may also be independently linked to one or more PEG radicals (polyethylene glycol).

20 The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having a carbonyl group linked to hydrocarbyl group having 1 to 7 carbon atoms (branched or straight chain or cyclic) derived from an organic acid by removal of the hydroxyl group. For example C<sub>4</sub> acyl can include (CO)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and (CO)(CH<sub>2</sub>CH(CH<sub>3</sub>))<sub>2</sub>; similarly, C<sub>6</sub> acyl includes both (CO)(C<sub>6</sub>H<sub>13</sub>) and (CO)(C<sub>6</sub>H<sub>5</sub>). The term "Ac" as  
25 used herein, whether used alone or as part of a substituent group, means acetyl.

"Aryl" is a carbocyclic aromatic radical including, but not limited to,  
30 phenyl, 1- or 2- naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, OH, CN, mercapto, nitro, amino, cyano, optionally substituted C<sub>1</sub>-C<sub>8</sub>-alkyl, optionally substituted alkoxy, alkylthio, alkylsulfinyl,



alkylsulfonyl, alkyl-amino, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino, formyl, carboxyl, alkoxy carbonyl, alkoxy carbonyloxy, alkanoyloxy, phenyl, carbamoyl, carboxamide, di-lower alkylcarbamoyloxy, phenoxy carbonyloxy group, lower alkylenedioxy, benzyloxy, alkyl-CO-O-, alkyl-O-CO-, -CONH<sub>2</sub>, alkyl-O-CO-O-,  
 5 or alkyl-CO-NH-. Illustrative aryl radicals include, for example, phenyl,

naphthyl, biphenyl, indene () , indane () , fluorophenyl, difluorophenyl, benzyl, benzyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl,  
 10 dimethylcarbamylphenyl and the like. "Ph" or "PH" denotes phenyl.

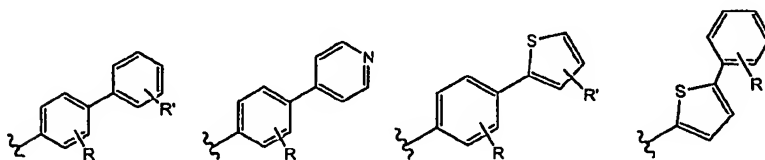
The term "heteroaryl" as used herein represents a stable five or six-membered monocyclic or bicyclic aromatic ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O and S.  
 15 The heteroaryl group may be attached at any heteroatom or carbon atom, which results in the creation of a stable structure. Examples of heteroaryl groups include, but are not limited to benzofuranyl, benzothiophenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, thiophenyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, benzimidazolyl,  
 20 benzofuranyl, benzothienyl, benzisoxazolyl, benzoxazolyl, benzopyrazolyl, indolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl or quinolinyl. Preferred heteroaryl groups include pyridinyl, thiophenyl, furanyl, and quinolinyl. When the heteroaryl group is substituted, the heteroaryl group may have one to three substituents which are independently selected from halogen, OH, CN,  
 25 mercapto, nitro, amino, cyano, optionally substituted C<sub>1</sub>-C<sub>8</sub>-alkyl, optionally substituted alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkyl-amino, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino, formyl, carboxyl, alkoxy carbonyl, alkoxy carbonyloxy, alkanoyloxy, phenyl, carbamoyl, carboxamide, di-lower alkylcarbamoyloxy, phenoxy carbonyloxy group, lower alkylenedioxy, benzyloxy, alkyl-CO-O-,  
 30 alkyl-O-CO-, -CONH<sub>2</sub>, alkyl-O-CO-O-, or alkyl-CO-NH-.

The terms "heterocycle," "heterocyclic," and "heterocyclyl" refer to an optionally substituted, fully or partially saturated, aromatic or nonaromatic, cyclic group which is, for example, a 4- to 7-membered monocyclic, 7- to 11-membered (or 9- to 10-membered) bicyclic (or heterobicycyl), or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, or 3 heteroatoms selected from nitrogen atoms, oxygen atoms, and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The nitrogen atoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl; oxetanyl; pyrazolinyl; imidazolinyl; imidazolidinyl; oxazolyl; oxazolidinyl; isoxazolinyl; thiazolidinyl; isothiazolidinyl; tetrahydrofuryl; piperidinyl; piperazinyl; 2-oxopiperazinyl; 2-oxopiperidinyl; 2-oxopyrrolidinyl; 4-piperidonyl; tetrahydropyranyl; tetrahydrothiopyranyl; tetrahydrothiopyranyl sulfone; morpholinyl; thiomorpholinyl; thiomorpholinyl sulfoxide; thiomorpholinyl sulfone; 1,3-dioxolane; dioxanyl; thietanyl; thiiranyl; and the like. Exemplary bicyclic heterocyclic groups (or heterobicyclys) include quinuclidinyl; tetrahydroisoquinolinyl; dihydroisoindolyl; dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl); dihydrobenzofuryl; dihydrobenzothienyl; dihydrobenzothiopyranyl; dihydrobenzothiopyranyl sulfone; dihydrobenzopyranyl; indolinyl; isochromanyl; isoindolinyl; benzimidazolyl, benzthiazolyl; piperonyl; tetrahydroquinolinyl; and the like. When the heteroaryl group is substituted, the heterocyclyl may be independently substituted with one to five, preferably one to three groups selected from halogen, OH, CN, mercapto, nitro, amino, cyano, optionally substituted C<sub>1</sub>-C<sub>8</sub>-alkyl, optionally substituted alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkyl-amino, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino, formyl, carboxyl, alkoxycarbonyl, alkoxycarbonyloxy, alkanoyloxy, phenyl, carbamoyl, carboxamide, di-lower alkylcarbamoyloxy, phenoxycarbonyloxy group, lower alkylenedioxy,

benzoyloxy, alkyl-CO-O-, alkyl-O-CO-, -CONH<sub>2</sub>, alkyl-O-CO-O-, or alkyl-CO-NH-.

- The term "biaryl" includes a heteroaryl linked to a phenyl, a phenyl linked to a heteroaryl (such as furan, pyridine, thiophene), and a phenyl linked to a phenyl. Examples of phenyl-phenyl, heteroaryl-phenyl and phenyl-heteroaryl, include:



- The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

- The term "combined administration" includes co-administration wherein:
- 1) the two or more agents are administered to a subject at substantially similar times; and
  - 2) the two or more agents are administered to a subject at different times, at independent intervals which may or may not overlap or coincide.

- The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who is the object of treatment, observation or experiment.

- The term "RXR modulator" as used herein, refers to Retinoid-X receptor agonists, partial agonists, or antagonists. Preferably the modulator increases insulin sensitivity. According to one aspect, the modulator is an RXR agonist.

- Diabetes, Syndrome X, and associated symptoms or complications include such conditions as IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome,

hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts. Examples of a prediabetic state includes IGT and IFG.

5           Methods are known in the art for determining effective doses for therapeutic and prophylactic purposes for the disclosed pharmaceutical compositions or the disclosed drug combinations, whether or not formulated in the same composition. For therapeutic purposes, the term "jointly effective amount" as used herein, means that amount of each active compound or  
10   pharmaceutical agent, alone or in combination, that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. For prophylactic purposes (i.e., inhibiting the onset or progression of a disorder),  
15   the term "jointly effective amount" refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that inhibits in a subject the onset or progression of a disorder as being sought by a researcher, veterinarian, medical doctor or other clinician, the delaying of which disorder is mediated by the modulation of glucose reabsorption activity or other  
20   antidiabetic agent activity or both. Thus, the present invention provides combinations of two or more drugs wherein, for example, (a) each drug is administered in an independently therapeutically or prophylactically effective amount; (b) at least one drug in the combination is administered in an amount that is sub-therapeutic or sub-prophylactic if administered alone, but is  
25   therapeutic or prophylactic when administered in combination with the second or additional drugs according to the invention; or (c) both drugs are administered in an amount that is sub-therapeutic or sub-prophylactic if administered alone, but are therapeutic or prophylactic when administered together.

30

          The term "protecting groups" refer to those moieties known in the art that are used to mask functional groups; protecting groups may be removed during subsequent synthetic transformations or by metabolic or other in vivo

administration conditions. During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those  
5 described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known in the art. Examples of hydroxyl and diol protecting groups are provided  
10 below.

Protection for the hydroxyl group includes methyl ethers, substituted methyl ethers, substituted ethyl ethers, substituted benzyl ethers, and silyl ethers.

#### 15 *Substituted Methyl Ethers*

Examples of substituted methyl ethers include methoxymethyl, methylthiomethyl, *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, (4-methoxyphenoxy)methyl, *t*-butoxymethyl, 4-pentenylloxymethyl, siloxymethyl, 2-methoxyethoxymethyl,  
20 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxido, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl,  
25 tetrahydrofuranyl, tetrahydrothiofuranyl and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl.

#### *Substituted Ethyl Ethers*

Examples of substituted ethyl ethers include 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl, and polyethyleneglycol ethers.

*Substituted Benzyl Ethers*

Examples of substituted benzyl ethers include *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, *p*, *p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl,  $\alpha$ -naphthylidiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-ylmethyl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido.

*Silyl Ethers*

Examples of silyl ethers include trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

*Esters*

In addition to ethers, a hydroxyl group may be protected as an ester. Examples of esters include formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-P-phenylacetate, 3-phenylpropionate, 4-oxopentanoate(levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate(mesitoate), and polyethyleneglycol esters.

*Carbonates*

- Examples of carbonates include methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, methyl dithiocarbonate, and polyethyleneglycol carbonates.

*Assisted Cleavage*

- Examples of assisted cleavage include 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate, 4-(methylthiomethoxy)butyrate, and 2-(methylthiomethoxymethyl)benzoate.

15 *Miscellaneous Esters*

- Examples of miscellaneous esters include 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenolate(tigloate), *o*-(methoxycarbonyl)benzoate, *p*-P-benzoate,  $\alpha$ -naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, N-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate

25 *Sulfonates*

- Examples of sulfonates include sulfate, methanesulfonate(mesylate), benzyisulfonate, and tosylate.

30 PROTECTION FOR 1,2- AND 1,3-DIOLS*Cyclic Acetals and Ketals*

- Examples of cyclic acetals and ketals include methylene, ethylidene, 1-*i*-butylethylidene, 1-phenylethylidene, (4-methoxyphenyl)ethylidene, 2,2,2-

trichloroethylidene, acetonide (isopropylidene), cyclopentylidene, cyclohexylidene, cycloheptylidene, benzylidene, *p*-methoxybenzylidene, 2,4-dimethoxybenzylidene, 3,4-dimethoxybenzylidene, and 2-nitrobenzylidene.

5    *Cyclic Ortho Esters*

Examples of cyclic ortho esters include methoxymethylene, ethoxymethylene, dimethoxymethylene, 1-methoxyethylidene, 1-ethoxyethylidene, 1,2-dimethoxyethylidene,  $\alpha$ -methoxybenzylidene, 1-(*N,N*-dimethylamino)ethylidene derivative,  $\alpha$ -(*N,N*-dimethylamino)benzylidene derivative, and 2-oxacyclopentylidene.

10

*Silyl Derivatives*

Examples of silyl derivatives include di- *t*-butylsilylene group, and 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene) derivative.



## Glucose Reabsorption Inhibitors

One method of treating hyperglycemia is to excrete excessive glucose directly into urine so that the blood glucose concentration is normalized. For example, sodium-glucose cotransporters (SGLTs), primarily found in chorionic membrane of the intestine and the kidney, are a family of proteins actively involved in the normal process of glucose absorption. Among them, SGLT1 is present in intestinal and renal epithelial cells (Lee et al., 1994), whereas SGLT2 is found in the epithelium of the kidney (You et al., 1995, MacKenzie et al., 1994). Glucose absorption in the intestine is primarily mediated by SGLT1, a high-affinity low-capacity transporter with a Na<sup>+</sup>:glucose transport ratio of 2:1. SGLT2, also known as SAAT1, transports Na<sup>+</sup> and glucose at a ratio of 1:1 and functions as a low-affinity high-capacity transporter. These SGLTs are characterized in Table 1:

Table 1

ISOFORM	TISSUE	Stoichiometry	Preferred Substrate	K <sub>m</sub> * in vitro	TmG** in vitro	K <sub>m</sub> * In vivo
SGLT1	Sm. Intestine	2:1	D-glucose D-galactose	0.1	nd	Nd
	Kidney (S1, S3)	2:1	D-glucose D-galactose	0.39	7.9	0.3
SGLT2 (SAAT1)	Kidney (S3)	1:1	D-glucose	1.64	83	6

\* (mM) for D-glucose

\*\* Maximal transport rate pmol/min/mm

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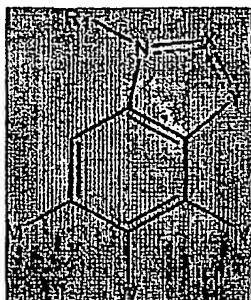
1. Renal reabsorption of glucose is mediated by SGLT1 and SGLT2 (Silverman et al., 1992; Deetjen et al., 1995). Plasma glucose is filtered in the glomerulus and is transepithelially reabsorbed in the proximal tubules. SGLT1 and SGLT2 are located in the apical plasma membranes of the epithelium and derive their energy from the inward sodium gradient created by the Na<sup>+</sup>/K<sup>+</sup> ATPase pumps located on the basolateral membrane. Once reabsorbed, the elevated cytosolic glucose is then transported to the interstitial space by facilitated glucose transports (GLUT1 and GLUT2). Therefore, inhibition of SGLTs reduces plasma glucose through suppression of glucose reabsorption

in the kidney. A therapeutically or prophylactically effective amount of an SGLT inhibitor, such as that sufficient to increase urine glucose excretion, or to decrease plasma glucose, in a subject by a desired amount per day, can be readily determined using methods established in the art. Recently, it has been  
5 found that phlorizin, a natural glycoside present in barks and stems of *Rosaceae* (e.g., apple, pear, etc.), inhibits  $\text{Na}^+$ -glucose co-transporters located in chorionic membrane of the intestine and the kidney. By inhibiting  $\text{Na}^+$ -glucose co-transporter activity, phlorizin inhibits the renal tubular glucose reabsorption and promotes the excretion of glucose so that the glucose level in  
10 a plasma is controlled at a normal level for a long time via subcutaneous daily administration (Journal of Clinical Investigation, 1987, Vol. 79, p. 1510).

Other SGLT inhibitors include alkyl- and phenyl-glucosides, 1-5-isoquinolinesulfonyl)-2-methylpiperazine-HCl (indirectly via protein kinase C), p-  
15 chloromercuribenzoate (PCMB), N,N'-dicyclohexylcarbodiimide (DCCD), copper and cadmium ions, and trivalent lanthanides.

## B. Compounds

The invention features compounds of Formula (IV):



(IV)

5

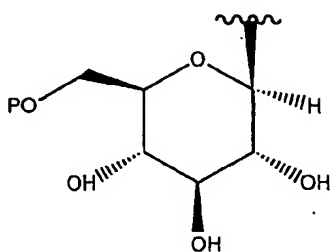
wherein:

one of the dashed lines between  $NR_1$  and X or between X and Y is present, or

both are absent;

two of V, M, and W are H and the third is

10



$R_1$  is H, or  $C_{1-4}$  alkyl; or  $R_1$  is absent where the dashed line between  $NR^1$  and X is present,

15

X is N, C=O, CH, or C-Q-Z;

Y is N-Q-Z or C-Q-Z, where X is N, C=O, or CH;

Y is CH, where X is C-Q-Z;

20

Q =  $-(CH_2)_n-$  where  $n = 1$  or  $2$ ;

Z is substituted or unsubstituted, and is selected from C<sub>3-7</sub> cycloalkyl, phenyl, a 5- or 6- membered heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, a biaryl, a 9- or 10-membered fused bicycyl (such as naphthyl), and a fused heterobicycyl, wherein said fused heterobicycyl has  
 5 between 1 and 4 heteroatoms (and preferably between 1 and 3 or between 1 and 2 heteroatoms) independently selected from N, O, and S;

P = H, C<sub>1-7</sub> acyl, or (C<sub>1-6</sub> alkoxy)carbonyl;

10 or a pharmaceutically acceptable salt, thereof.

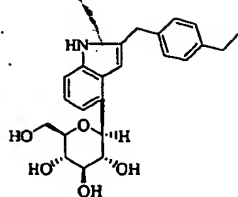
Examples of preferred compounds of Formula (IV) include: (a) R<sub>1</sub> is H or absent; (b) Z is independently substituted with between 1 and 3 substituents independently selected from C<sub>1-4</sub> alkoxy, phenoxy, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl,  
 15 halo, hydroxy, cyano, amino, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> aminoalkyl, mono and di C<sub>1-4</sub> alkylamino, phenyl, C<sub>1-4</sub> alkylaminosulfonyl (SO<sub>2</sub>NHR), amino(C<sub>1-4</sub> alkylsulfonyl) (NHSO<sub>2</sub>R), di C<sub>1-4</sub> alkylaminosulfinyl (SONHRR), C<sub>1-4</sub> alkylamido (NHCOR), C<sub>1-4</sub> alkylcarbamido (CONHR), 5-6 membered heterocyclyl containing between 1 and 3 heteroatoms  
 20 independently selected from N, S, and O; and wherein the substituent(s) on Z can be further independently substituted with between 1 and 3 substituents independently selected from C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl, halo, hydroxy, cyano, amino, mono or di C<sub>1-4</sub> alkyl amino and C<sub>1-4</sub> alkylthio; (c) Z is 4-substituted phenyl, 3,4-disubstituted phenyl, benzhydryl, substituted or unsubstituted  
 25 thienyl, biaryl, benzofuranyl, dihydrobenzofuranyl, 4-substituted pyridyl, benzo[b]thienyl, chromanyl, benzothiophenyl, indanyl, naphthyl, and 2,3-dihydro-benzo[1,4] dioxan; (d) limitations of (c) wherein Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl; (e) Z  
 30 is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl, (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl; (f) R<sub>1</sub> is H; (g) n is 1; (h) R<sub>1</sub> is H or absent, and n is 1; (i) Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-imidazole-1-

yl)-phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl, (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl; and Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl; (j) limitations of (i) and R<sub>1</sub> is H; (k) limitations of (i) and n is 1; (l) W and M are H; (m) V and M are H; (n) X is CH and Y is C-Q-Z; (o) X is C-Q-Z and Y is CH; (p) and combinations of the above.

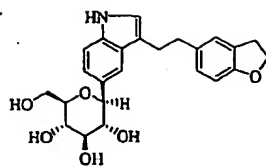
Preferred examples of compounds of the invention include:

10 3-(4-Ethylbenzyl)-5-( $\beta$ -D-glucopyranosyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-(4-methoxybenzyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole; and 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole.

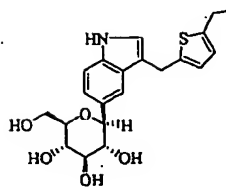
Additional preferred compounds include those selected from 2-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole; 3-[2-(2,3-Dihydro-benzofuran-5-yl)-ethyl]-5-( $\beta$ -D-glucopyranosyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-(5-ethyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzimidazole; 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1,3-dihydro-benzimidazol-2-one and 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzotriazole.



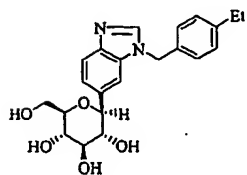
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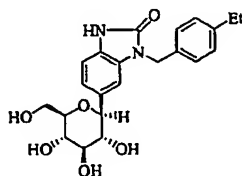
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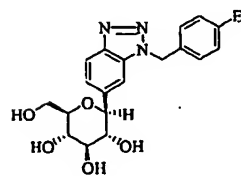
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The most preferred compounds are selected from: 3-(4-Ethylbenzyl)-5-( $\beta$ -D-glucopyranosyl)-1H-indole; 2-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole;  
 5 5-( $\beta$ -D-Glucopyranosyl)-3-(5-methyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzimidazole and 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzotriazole.

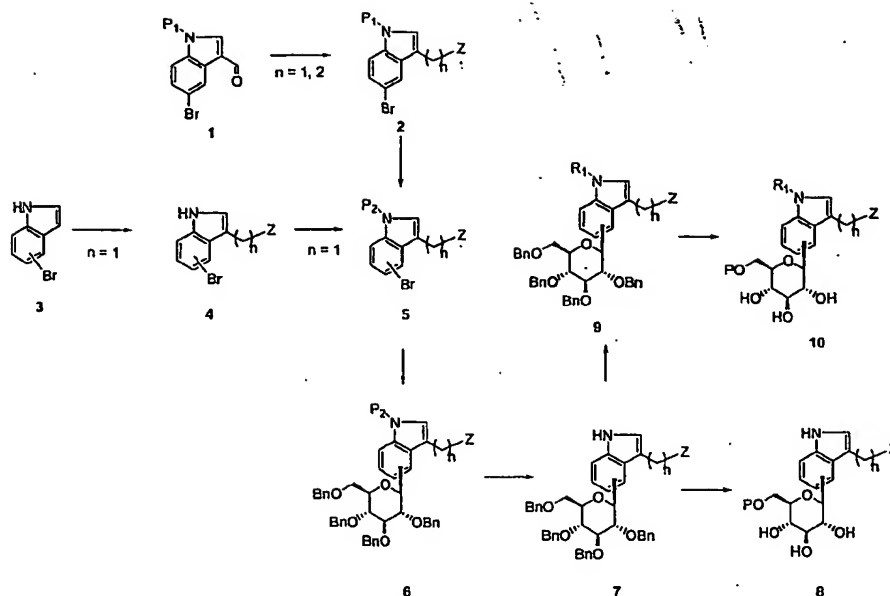
### C. Synthetic Methods.

10

One aspect of the invention features compounds of formula (IV). These compounds can be made according to traditional synthetic organic methods or combinatorial or matrix synthesis methods. The following schemes and chemical Examples 1-4 provide general guidance.

15

Scheme 1.



- Compounds of this invention where X is C-H, Y is C-Q-Z (e.g. 3-alkyl indole) can be prepared as outlined in Scheme 1. Compounds of formula 1 wherein
- 5 R<sub>3</sub> is H and P<sub>1</sub> is N,N-diethylcarbamyl can be prepared by treatment of the sodium salt of commercially available 5-bromo-1H-indole-3-carboxaldehyde with N,N-diethylcarbamyl chloride in anhydrous THF. The protected indole may be treated with ylides under standard Wittig reaction conditions to provide an E/Z mixture of compounds. Hydrogenation of the alkene over
- 10 Platinum(IV)oxide (Adam's catalyst) in a chlorinated solvent at 1 atmosphere provides compounds of formula 2, wherein n is 2. A compound of formula 1 can also be treated with an aryl magnesium bromide in THF to give an indolecarbinol. The crude indolecarbinol can be reduced with triethylsilane and stannic chloride in dichloromethane at -78 °C to provide compounds of formula
- 15 2, wherein n is 1. The indole nitrogen of compounds of formula 2, where n is 1 or 2, can be deprotected by treatment with an aqueous base such as sodium hydroxide in refluxing ethanol to remove the N,N-diethylcarbamyl group followed by reprotection with *tert*-butyldimethylsilyl (TBDMS) group (P<sub>2</sub>) by treatment with *tert*-butyldimethylsilyl chloride using known procedures to yield
- 20 5-bromo indole derivative 5.

Alternatively, a compound of formula 5, where n is 1 (either 4-bromoindole derivatives or 5-bromoindole or 6-bromoindole derivatives), can be prepared in three steps from commercial available sources of formula 3. Friedel-Craft  
5 acylation of compounds of formula 3 with substituted benzoyl chlorides using a Lewis Acid, such as aluminum trichloride, in a chlorinated solvent, such as dichloromethane, followed by reduction of the carbonyl group with sodium borohydride to provide compounds of formula 4. The indole nitrogen of formula 4 can be protected with TBDMS group as described above to give  
10 compounds of formula 5, where n is 1.

Compounds of formula 5 are activated for coupling by treatment with t-BuLi at -78 °C in a solvent such as THF prior to addition of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone as described by Czernecki and Ville [J. Org. Chem. 1989, 53, 610  
15 - 612]. The resulting lactol can be treated with silanes such as triethylsilane in a solvent such as dichloromethane at -30 °C to provide compounds of formula 6. The TBDMS group can be removed with an aqueous base such as sodium hydroxide in refluxing THF to yield compounds of formula 7. Hydrogenolysis of glucopyranose 7 over palladium hydroxide (Pearlman's catalyst) at one  
20 atmosphere can provide compounds of formula 8 where P is H.

The sodium salt of 7 can be treated with an alkyl halide to give the N-alkylated (R<sub>1</sub>) product 9, which was undergone hydrogenolysis as previously described to provide compound of formula 10 where P is H.

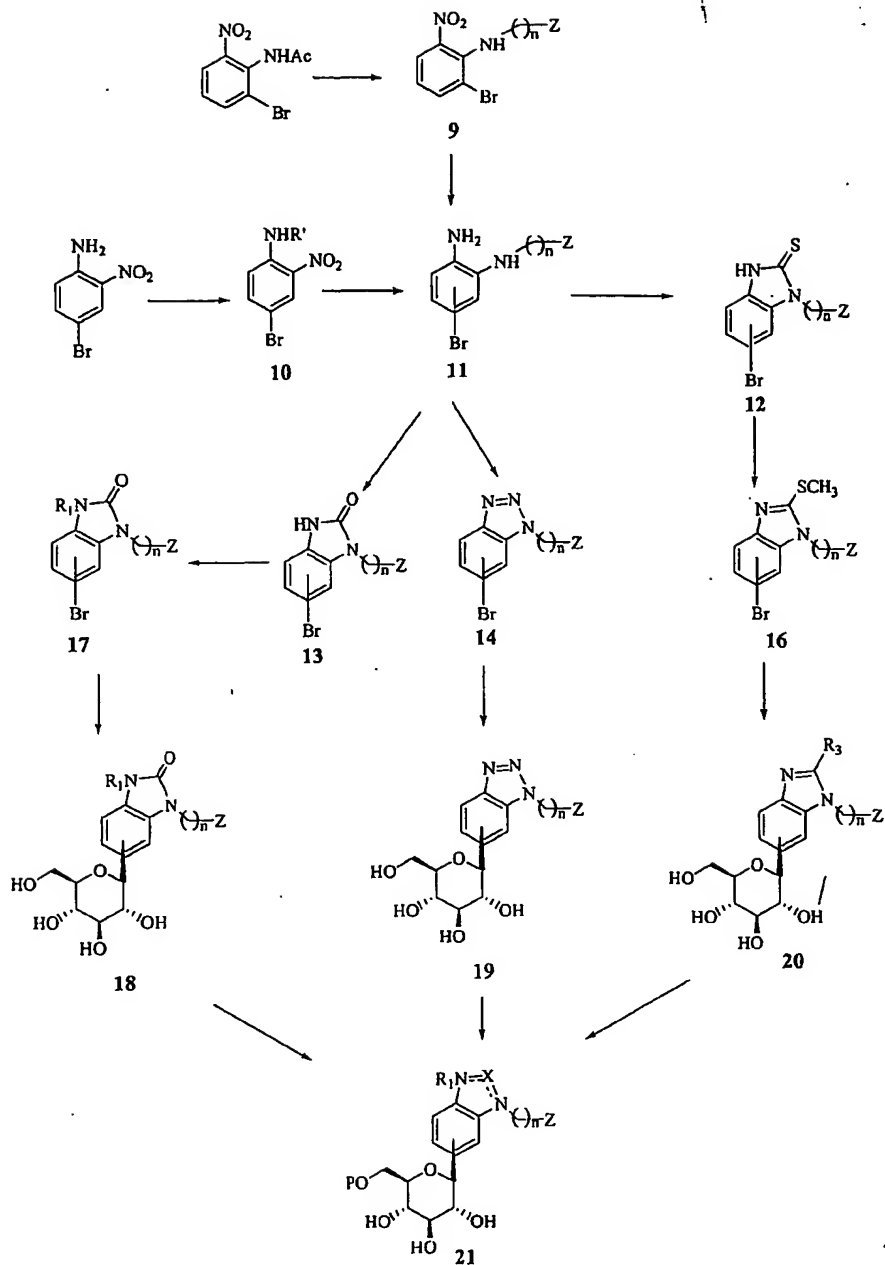
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Further treatment of compounds of formula 8 or 10, where P is H, with one equivalent of alkyl chloroformate or alkanoyl chloride in collidine to selectively acylate the 6-OH group of the glucopyranose can provide compounds of formula 8 or 10, where P is acyl, or alkoxycarbonyl.

30



Scheme 2



Compounds of this invention wherein Y is N-Q-Z, X is N, C=O or C-H, and R<sub>1</sub> is  
 5 as defined in the claims above could be prepared as outlined in Scheme 2

using procedures known in the art for the synthetic transformations described. Commercially available N-(2-Bromo-6-nitro-phenyl)-acetamide could be heated under acidic condition to remove the acetyl group then alkylated with substituted benzyl, aryl or heteroaryl alkyl halides, acylated with benzoyl or phenylacetyl chlorides followed by LAH or borane reduction or reductively aminated with substituted benzaldehydes in the presence of sodium cyanoborohydride to provide compounds of formula 9. The nitro group could then be reduced using reagents such as tin (II) chloride or iron in acetic acid to obtain compounds of formula 11 wherein the bromine is attached at position V in claim 1.

Alternatively, one could start with commercially available 4-Bromo-2-nitroaniline, introduce the side-chain containing Z as described above to afford compounds of formula 10 where R' is  $-(CH_2)_nZ$  then reduce the nitro group to provide compounds of formula 11 wherein the bromine is attached at position M in claim 1.

On the other hand, the aniline nitrogen of commercially available 4-Bromo-2-nitroaniline could be acetylated or alternatively protected with an appropriate protecting group such as toluenesulfonyl or benzenesulfonyl to yield compounds of formula 10 wherein R' is the protecting group. The nitro group could then be reduced to a primary amine with tin (II) chloride and subsequently alkylated by treatment with substituted benzyl, aryl or heteroaryl alkyl halides, under basic conditions or reductively aminated with substituted benzaldehydes in the presence of sodium cyanoborohydride. Alternatively the primary amine could be acylated with benzoyl or phenylacetyl chlorides followed by LAH or borane reduction. Final removal of the nitrogen protecting group using procedures known in the art could provide compounds of formula 11 wherein the bromine is attached at position W in claim 1.

Compounds of formula 11 could be reacted further to form compounds of formula 12, 13, and 14. These transformations can be accomplished by

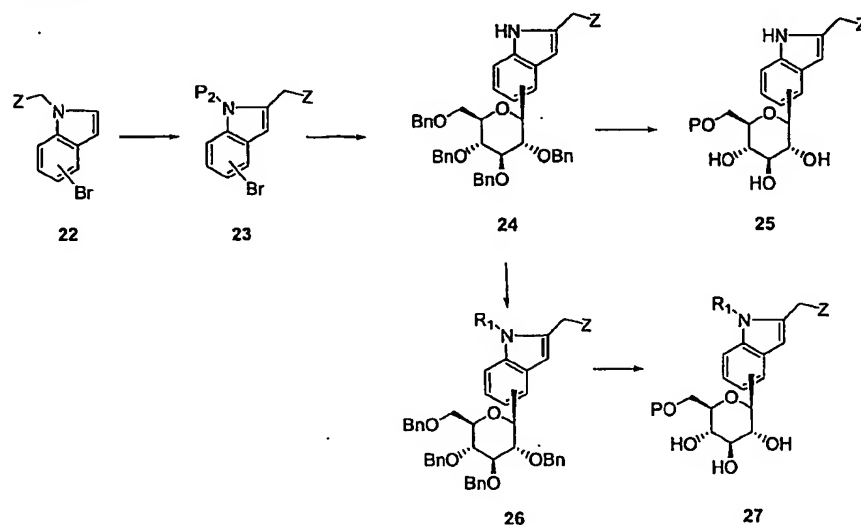
treating the diamine with 1,1'-thiocarbonyldiimidazole or carbon disulfide to provide compound of formula 12 or with triphosgene, urea or carbonyldiimidazole to give compounds of formula 13. Alternatively, the diamine 11 could be treated with sodium nitrate under acidic conditions at cool  
5 temperatures to provide compounds of Formula 14.

Methylation of compounds of formula 12 with iodomethane in the presence of a base can afford compounds of formula 16. Compounds of formula 13 can be treated with base such as sodium hydride and alkylated with alkyl halides to  
10 provide compounds of formula 17 wherein R<sub>1</sub> is alkyl. The unsubstituted nitrogen of compound of formula 13 can also be protected with an alkoxy carbonyl group as described by Meanwell et. al. [J. Org. Chem. 1995, 60, 1565 – 1582] to provide compounds of formula 17 wherein R<sub>1</sub> is either an ethoxy carbonyl moiety or a t-butoxycarbonyl group.

15 Formation of the C-glycosides can be accomplished by treating compounds of formula 14, 16 or 17 (compound 15 is omitted) with butyllithium at –78 °C prior to the addition of 2,3,4,6-tetra-O-benzyl-β-D-glucolactone followed by reduction of the resulting hemiacetal in the presence of excess triethylsilane and boron trifluoride diethyl etherate in an appropriate solvent such as dichloromethane  
20 as described by Czernecki and Ville (J. Org. Chem. 1989, 54, 610 – 612). Compounds of formula 18, wherein R<sub>1</sub> is H, can be prepared by removing the protection groups under basic condition (for ethoxy carbonyl group) or under acidic condition (for tert-butoxycarbonyl group) followed by debenzylation of the  
25 hydroxyl groups using palladium catalysts under hydrogenation conditions. Compounds of formula 18, wherein R<sub>1</sub> is an alkyl group, or formula 19 can be formed by debenzylation of the hydroxyl groups using palladium catalysts under hydrogenation conditions. Compounds of formula 20 wherein R<sub>3</sub> is H can be prepared by a Raney nickel mediated cleavage of the 2-methylthio  
30 group as described by Townsend, et. al. (J. Med. Chem. 1994, 37, 2942 – 2949) followed by debenzylation of the hydroxyl groups using palladium catalysts under hydrogenation conditions.

Further treatment with one equivalent of alkyl chloroformate or alkanoyl chloride in collidine to selectively acylate the 6-OH group of the glucopyranose can provide compounds of formula 21 where P is acyl, or alkoxycarbonyl.

5 Scheme 3.



Compounds of this invention where X is C-Q-Z and Y is CH (e.g. 2-alkyl indole) as defined in the claims above can be prepared as outlined in Scheme 3.

- 10 Compounds of formula 22 can be prepared by treatment of the sodium salt of commercially available bromoindoles (either 4-bromoindole or 5-bromoindole or 6-bromoindole) with an alkyl halides in anhydrous THF. The resulting N-alkyl indole can be rearranged to 2-alkyl indole at 180 °C in polyphosphoric acid under microwave condition, followed by protection of indole nitrogen with
- 15 TBDMS group ( $P_2$ ) to provide compounds of formula 23.

- Formation of the C-glycosides can be accomplished by treating compounds of formula 23 with butyllithium at  $-78^\circ\text{C}$  prior to the addition of 2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucolactone as described in Scheme 1. The resulting lactol can be
- 20 treated with silanes, such as triethylsilane, in a solvent such as dichloromethane at  $-30^\circ\text{C}$ , followed by deprotection of the TBDMS group with

an aqueous base, such as sodium hydroxide, in refluxing THF to yield compounds of formula 24.

- Hydrogenolysis of glucopyranose 24 over palladium hydroxide (Pearlman's catalyst) at one atmosphere can provide compounds of formula 25 where P is H. The sodium salt of 24 can be treated with an alkyl halide to give the N-alkylated (R<sub>1</sub>) product 26, followed by hydrogenolysis as previously described to provide compound of formula 27 where P is H.

#### 10 D. Additional Antidiabetic Agents

- Antidiabetic agents that can be used according to the invention, as a second, third, or subsequent antidiabetic agent, in a composition, formulation, or combination method of treatment (dosing regimen) include, but are not limited to the classes and compounds exemplified in Table 2.

Table 2  
Combination Therapies with SGLT Inhibitors

20

Mechanism or Class	Drug/Compound
Biguanide (class)	metformin
	Fortamet (metformin XT)
	metformin GR
	metformin XL
	NN-414
	fenofibrate/metformin combo
Insulin Secretagogue (mech), Sulfonylureas (class)	glimepiride
	glyburide/glibenclamide combo
	glyburide/metformin combo
	glipizide
	glipizide/metformin combo
	glizalide
	chlorpropamide
	tolbutamide
	tolazamide
Insulin Secretagogue (mech), Meglitinides (class)	repaglinide
	nateglinide
	mitiglinide
Alpha-glucosidase inhibitors (mech)	acarbose
	miglitol
	voglibose

	emiglitate
Insulin and Insulin analogues (class)	insulin lispro
	insulin glargine
	insulin detemir
	insulin glulisine
	insulin aspart
	human insulin (Humulin R)
	human insulin (Novolin R)
	human insulin (Novolin BR)
	insulin, zinc suspension (Humulin L)
	insulin NHP (Humulin N)
	insulin, zinc suspension (Novolin L)
	insulin NHP (Novolin N)
	insulin, zinc suspension (Humulin U)
	human insulin, regular and NHP mix (Humulin 50/50)
	human insulin, regular and NHP mix (Humulin 70/30)
	human insulin, regular and NHP mix (Novolin 70/30)
Inhaled insulin (class)	Exubera
	AERx Insulin Diabetes Management System
	AIR inhaled insulin
Oral insulin (class)	Oralin
PPARgamma (mech)	rosiglitazone
	rosiglitazone/metformin combo
	pioglitazone
	isaglitazone (netoglitazone, MCC-555)
	rosiglitazone/sulfonylurea
	ragaglitazar
	balaglitazone (NN-2344)
	R-483
	rivoglitazone (CS-011)
	FK-614
	SCD-DKY
	tesaglitazar
	T131
	CLX0921
	LY-293111 (VML-295)
	MBX 102
	AA10090
	CDDO (TP-155C)
	DRF-2189
	PHT-46
	farglitazar
	GW-7845
	L-764406
	NC-2100
	PN 2022 (PN 2034)
PPARalpha/gamma dual agonists (mech)	MK767/MK0767 (KRP 297)
	muraglitazar (BMS-298585)
	tesaglitazar
	LY-818
	oxeglitazar (EML-4156)
	LY-929

	BVT-142
	DRF-2655
	DRF-4832
	DRF-4158
	LY-465608
	KT6-207
	LSN-862
PPARalpha Agonist (mech)	Fenofibrate
	Gemfibrozil
	Clofibrate
	Ciprofibrate
	Benzafibrate
	K-111
	LY518674 (LY674)
	KRP-101
	NS-220
	GW-9578
	GW-7647
	GW-9820
	LF-200337
	ST-1929
	Wy-14643
PPARdelta Agonist (mech)	GW501516
	GW-1514
	L-165041
	GW 8547
PPARalpha/delta Dual Agonist (mech)	GW-2433
PPARgamma/delta Dual Agonist (mech)	none in the last PPAR CEA
PPARalpha/gamma/delta Modulator (mech)	CLX-0940
RXR Agonist (mech)	
Insulin Seretagogue (mech), GLP-1 analogue (class)	Exanatide injectable
	Exanatide LAR injectable
	Exanatide oral
	Liraglutide
GLP-1 agonist (mech)	exenatide (AC2993)
	liraglutide (NN2211)
	LY-307161
	CJC-113
	ZP10
	GLP-1
	BIM-51077
DPPIV Inhibitor (mech)	LAF-237
	P32/98
	P93/01
	NVP-728
Lipase Inhibitor (mech)	Orlistat
	ATL962
Glucokinase Activator (mech)	Ro 28-1675
	Ro 27-4375
beta-3 Agonist (mech)	LY-337604
	L-796568

	CP-331684
	CP-331679
	CP-114271
	Rafabegron (TAK-677)
	YM-178
	N5984
	GW427353
IBAT Inhibitor (mech)	AZD-7806
	SC-990
	SC-017
	GW-264
HM74a/HM74 Agonist (mech)	Acipimox
Glucocorticoid Antagonist (mech)	A348441
	A362947
	CP394531
	CP409069
	CP472555
Glycogen Phosphorylase a Inhibitor (mech)	NN4201
	Ingliforib (CP368296)
FXR Antagonist (mech)	GW-4064
LXR Agonist (mech)	GW-3965
	T-0901317
	T-0314407
FXR Antagonist (mech)	
GLP-1 Analogue (class)	Albugon
GSK-3beta Inhibitor (mech)	
PTP-1b Inhibitor (mech)	ISIS-113715
	KP102
Amylin Receptor Agonist	Pramlintide (symlin/amylin)
NO Scavenger (mech)	NOX-700
11beta-Hydroxysteroid Dehydrogenase Inhibitor	BVT-3498
Peptide YY hormone	AC162325
Glucagon Antagonist (mech)	NN-2501
PEPCK Inhibitor (mech)	R1438
Somatotropin Release-Inhibiting Factor (mech)	SOM230
CPT-1 Inhibitor (mech)	ST1326
Carboxypeptidase Inhibitor (mech)	MLN-4760
Leptin analogue (class)	Metrileptin



## E. Combinations

The invention features a combination therapy comprising administering  
5 a glucose reabsorption inhibitor, such as an SGLT inhibitor, and one or more  
antidiabetic agent(s) for the treatment of diabetes or Syndrome X, or  
associated symptoms or complications thereof. The demonstrated efficacy of  
SGLT inhibitors in numerous models of NIDDM validates the utility of this drug  
alone for the treatment of NIDDM in humans. Since glucose reabsorption  
10 inhibitors have a mechanism of action distinct from that of other antidiabetic  
agents, such as RXR modulators, the disclosed combination may have the  
advantage of reducing the amount of either drug necessary to achieve  
combined therapeutic or pharmaceutical efficacy, relative to the use of either  
drug alone, thereby reducing one or more adverse side-effects, which often  
15 include weight gain, edema, cardiac hypertrophy, hepatohypertrophy,  
hypoglycemia, or hepatotoxicity, or any combination thereof.

The invention provides a method for treating diabetes or Syndrome X, or  
complications thereof in a subject, said method comprising administering to  
20 said subject a jointly effective amount of a glucose reabsorption inhibitor in  
combination with a jointly effective amount of an antidiabetic agent, such as an  
RXR modulator. In one aspect of the invention, the antidiabetic agent is an  
RXR agonist or RXR antagonist that increases insulin sensitivity in the subject.  
For example, an insulin sensitizer can increase glucose tolerance in a subject  
25 in an oral glucose tolerance test.

Preferably, the diabetes or Syndrome X, or associated symptoms or  
complication thereof is selected from IDDM, NIDDM, IGT, and IFG.

This invention also provides a pharmaceutical composition comprising  
30 one or more glucose reabsorption inhibitors ( alone or in combination with one  
or more antidiabetic agents), and a pharmaceutically acceptable carrier. In one  
aspect of the invention, the antidiabetic agent is an RXR agonist or RXR  
antagonist that increases insulin sensitivity in the subject.

In particular, the glucose reabsorption inhibitor is a SGLT1 and/or SGLT2 inhibitor.

5           For use in medicine, the salt or salts of the compounds of Formula (IV) refer to non-toxic "pharmaceutically acceptable salt or salts." Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, 10   hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pantoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative basic/cationic salts include, 15   but are not limited to, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, or zinc. The compounds of Formula (IV) or a pharmaceutically acceptable salt thereof, may include an intramolecular salt thereof, or a solvate or hydrate thereof.

20

## F. Administration, Formulation, and Dosages

The utility of the disclosed compounds, compositions, and combinations to treat disorders in glucose and lipid metabolism can be determined according to the procedures well known in the art (see the references listed below), as well as all the procedures described in US PATENT NOs. 5424406, 5731292, 5767094, 5830873, 6048842, WO01/16122 and WO01/16123 which are incorporated herein by reference. The compound may be administered to a patient by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral administration. Preferably, formulations are for oral administration.

The present invention also provides pharmaceutical compositions comprising one or more glucose reabsorption inhibitors and one or more RXR modulators in association with a pharmaceutically acceptable carrier.

The daily dosage of the products may be varied over a wide range from 1 to 1000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 or 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 2 times per day. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly

administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient or ingredients are mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of one or more glucose reabsorption inhibitors and one or more antidiabetic agents, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient or ingredients are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient or ingredients of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include

synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin. The liquid forms in suitably flavored suspending or dispersing agents may also include the synthetic and natural gums, for example, tragacanth, 5 acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

10 Advantageously, the combinations of one or more glucose reabsorption inhibitors of the present invention, alone or in combination with one or more additional antidiabetic agents, may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, one or more glucose reabsorption inhibitors 15 and/or one or more antidiabetic agents according to the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent 20 throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and 25 the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, 30 magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Wherein the present invention is directed to the administration of a combination, the compounds may be co-administered simultaneously, sequentially, or in a single pharmaceutical composition. Where the compounds are administered separately, the number of dosages of each  
5 compound given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently.

Optimal dosages to be administered may be readily determined by  
10 those skilled in the art, and will vary with the particular compound used, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

15

The novel compositions of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of lipids, including but not limited to  
20 amphipathic lipids such as phosphatidylcholines, sphingomyelins, phosphatidylethanolamines, phosphatidylcholines, cardiolipins, phosphatidylserines, phosphatidylglycerols, phosphatidic acids, phosphatidylinositols, diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, and stearylamine, neutral lipids such as  
25 triglycerides, and combinations thereof. They may either contain cholesterol or may be cholesterol-free.

From Formula (IV) and other disclosed formulae it is evident that some compounds in the compositions of the invention may have one or more  
30 asymmetric carbon atoms in their structure. It is intended that the present invention include within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure isomeric forms may be obtained by the application of art known principles.

Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereospecific reactions.

Some compounds in the compositions of the present invention may have various individual isomers, such as trans and cis, and various alpha and beta attachments (below and above the plane of the drawing). In addition, where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared as a single stereoisomer or in racemic form as a mixture of some possible stereoisomers. The non-racemic forms may be obtained by either synthesis or resolution. The compounds may, for example, be resolved into their components enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation. The compounds may also be resolved by covalent linkage to a chiral auxiliary, followed by chromatographic separation and/or crystallographic separation, and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using chiral chromatography. Unless otherwise noted, the scope of the present invention is intended to cover all such isomers or stereoisomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

The therapeutic effect of the glucose reabsorption inhibitor administered in combination with one or more antidiabetic agent(s) in treating diabetes, Syndrome X, or associated symptoms or complications can be shown by methods known in the art. The following examples of combination treatment with SGLT inhibitors and other antidiabetic agents such as RXR modulators are intended to illustrate the invention but not to limit it.

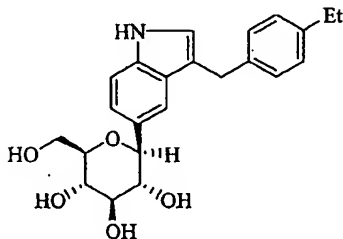
## G. Synthetic Chemical Examples.

One aspect of the invention features compounds of formula (IV) as described above in the Summary section, the description, and the appended claims. These disclosed compounds may be made according to traditional  
5 synthetic organic chemistry methods or according to matrix or combinatorial chemistry methods. The Schemes and Examples 1-9 below provide general guidance and detailed examples of how the disclosed compounds may be prepared.

10 <sup>1</sup>HNMR spectra were measured on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard.

Example 1

3-(4-Ethylbenzyl)-5-(β-D-glucopyranosyl)-1H-indole



15

- A. 5-Bromo-3-formyl-indole-1-carboxylic acid diethylamide: To a suspension of sodium hydride (0.93 g, 37 mmol) in anhydrous THF (75 mL) was added dropwise a solution of 5-bromo-1H-indole-3-carbaldehyde (7.5 g, 34 mmol) in anhydrous THF (60  
20 mL) at 0 °C. After stirring at 0 °C for 15 min, N,N-diethylcarbonyl chloride (5.0 g, 37 mmol) was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was crystallized  
25 from ether/hexane to give the title compound (8.75 g, 80%) as a white solid.
- B. 5-Bromo-3-(4-ethyl-benzyl)-indole-1-carboxylic acid diethylamide: To a solution of Part A (3.3 g, 10 mmol) in 20 mL of anhydrous THF was added dropwise a 0.5 M solution of 4-ethylphenylmagnesium bromide in anhydrous THF (22 mL, 11 mmol) at



0 °C. The reaction mixture was continued stirring at 0° C for 30 min, quenched with a saturated ammonium chloride solution and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated in vacuo. The crude product was used directly in the next step.

5 To a solution of the crude indolecarbinol in 20 mL of dichloromethane was added triethylsilane (1.16 g, 10.0 mmol) at -78° C, followed by addition of a 1.0 M solution of stannic chloride in dichloromethane (20 mL, 20 mmol). The reaction mixture was continued stirring at -78° C for 20 min, quenched with water and warmed to room temperature. After extraction with dichloromethane, the organic extracts were  
10 dried over sodium sulfate, concentrated in vacuo and chromatographed with silica gel eluting with ethyl acetate/hexane (10: 100) to provide the titled compound (3.4 g, yield: 82%) as a white solid.

C. 5-Bromo-3-(4-ethyl-benzyl)-1H-indole: The compound prepared in Part B (3.4 g, 8.2 mmol) was dissolved in ethanol (60 mL) and 25% aqueous sodium hydroxide  
15 (20 mL) and the resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (60 mL), concentrated in vacuo to remove most of ethanol, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with  
20 ethyl acetate / hexane (1:4) to provide the title compound (2.0 g, 79%) as white needle crystals.

D. 5-Bromo-1-(tert-butyl-dimethyl-silanyl)-3-(4-ethyl-benzyl)-1H-indole: To a suspension of sodium hydride (0.12 g, 4.8 mmol) in anhydrous THF (2 mL) was added dropwise a solution of the compound prepared in Part C (1.28 g, 4.0  
25 mmol) in anhydrous THF (6 ml) at 0° C. After stirring at 0° C for 30 min, a 1.0M solution of tert-butyl-chloro-dimethyl-silane in anhydrous THF (4.5 mL, 4.5 mmol) was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water and extracted with ethyl acetate. The organics were  
30 washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (0.5:100) to provide the title compound (1.75 g, 100%) as a light yellow oil.

E. 3-(4-Ethylbenzyl)-5-(2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucopyranosyl)-1-(tert-butyl-dimethyl-silyl)-1H-indole: To a stirred solution of the compound prepared in Part D (1.75 g, 4.0 mmol) in dry THF (2 mL) at  $-78^{\circ}\text{C}$  was added a 1.7 M solution of tert-butyl lithium in heptane (4.7 mL, 8.0 mmol) over a period of 15 min. After stirring 30 min, a solution of 2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucolactone (4.3 g, 8.0 mmol; prepared as described by Benhaddou, R.; Carbohydrate Research 1994, 260, 243 – 250) in dry THF (10 mL) was added at  $-78^{\circ}\text{C}$  over a period of 15 min. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 hr (reaction progress was monitored by TLC). Upon completion the reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL), warmed to room temperature and the reaction mixture was diluted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide a mixture of the desired lactol and unreacted 2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucolactone (2.8 g, ~50% of the desired lactol) as a light brown oil. This mixture was used directly to the next step without further purification.

To a solution of the above mixture (2.8 g) in dichloromethane (20 mL) was added triethylsilane (0.5 mL, 3.2 mmol) at  $-30^{\circ}\text{C}$ , followed by the addition of trifluoroborane diethyl ether (0.2 mL, 1.6 mmol). After stirring between  $-30$  to  $-20^{\circ}\text{C}$  for 1 hr, when TLC analysis indicated the reaction was completed, the reaction was quenched by addition of saturated aqueous  $\text{NaHCO}_3$  (3 mL). The mixture was warmed to room temperature and stirred for 1 hr. The reaction mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (0.68 g, 19% for two steps) as a yellow oil.

F. 3-(4-Ethylbenzyl)-5-(2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucopyranosyl)-1H-indole: Part E (0.68 g, 0.78 mmol) was dissolved in THF (15 mL) and 25% aqueous sodium hydroxide (5 mL) and the resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (30 mL), and extracted with ethyl acetate. The organic extracts were

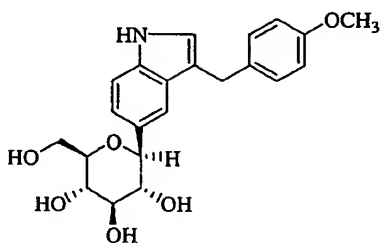
washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:3) to provide the title compound (0.5 g, 85%) as white solid.

- 5 G. 3-(4-Ethylbenzyl)-5-( $\beta$ -D-glucopyranosyl)-1H-indole: A solution of Part F (0.30 g, 0.4 mmol) in ethanol (10 mL) and ethyl acetate (20 mL) was hydrogenated over 10% Pearlman's catalyst (0.30 g) under 14 psi of H<sub>2</sub> for 40 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with methanol/chloroform (10:100) to provide the titled compound (0.04 g, 25%) as a white solid. <sup>1</sup>HNMR (300MHz, CD<sub>3</sub>OD)  $\delta$  7.51 (s, 1H), 7.32 (d, J = 8.52Hz, 1H), 7.19 - 7.15 (m, 3H), 7.06 (d, J = 7.87Hz, 2H), 6.95 (s, 1H), 4.18 - 4.15 (m, 1H), 4.04 (s, 2H), 3.87 (d, J = 12.2Hz, 1H), 3.71 - 3.65 (m, 1H), 3.53 - 3.48 (m, 2H), 3.45 - 3.41 (m, 2H), 2.58 (q, J = 7.58Hz, 2H), 1.19 (t, J = 7.65Hz, 3H). MS: m/z (M+Na) 420.

15

### Example 2

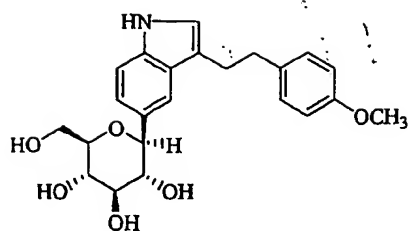
5-( $\beta$ -D-Glucopyranosyl)-3-(4-methoxybenzyl)-1H-indole



- The title compound was prepared as a white solid, from 5-bromo-3-formyl-indole-1-carboxylic acid diethylamide (Example 1, Part A) and 4-methoxyphenyl-magnesium bromide by the same procedure as described in Example 1, Part B to G). <sup>1</sup>HNMR (300MHz, CD<sub>3</sub>OD)  $\delta$  7.49 (s, 1H), 7.32 (d, J = 8.20Hz, 1H), 7.19 - 7.15 (m, 3H), 6.95 (s, 1H), 6.79 (d, J = 8.55Hz, 2H), 4.18 - 4.15 (m, 1H), 4.02 (s, 2H), 3.88 - 3.85 (m, 1H), 3.74 (s, 3H), 3.70 - 3.66 (m, 1H), 3.50 - 3.48 (m, 2H), 3.42 - 3.35 (m, 2H). MS: m/z (M+Na) 422.

### Example 3

5-( $\beta$ -D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole



A. 5-Bromo-3-[2-(4-methoxy-phenyl)-ethyl]-indole-1-carboxylic acid diethylamide:

To a solution of 4-methoxybenzyl triphenylphosphonium chloride (7.5 g, 18 mmol) in anhydrous THF (75 mL) at  $-78^{\circ}\text{C}$  was added LDA (9.0 mL, 18 mmol) and the resulting reaction mixture was allowed to stir at  $-78^{\circ}\text{C}$  for 1 h. Thereafter, 5-bromo-3-formyl-indole-1-carboxylic acid diethylamide (1.9 g, 6 mmol, Example 1, Part A) was added and the resulting reaction mixture was allowed to stir at  $-78^{\circ}\text{C}$  for 1 h and then warmed to room temperature to stir overnight. The reaction mixture was poured onto 1N HCl solution and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the mixture of alkenes (2.3 g, 90%, E:Z ~ 1:1) as a brown oil. A solution of the above alkenes (2.3 g, 5.4 mmol) in dichloromethane (100 mL) was hydrogenated over Adam's catalyst (300 mg) under  $\text{H}_2$  (15 psi) for 2 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (1.43 g, 62%) as a colorless oil.

B. 5-Bromo-3-[2-(4-methoxy-phenyl)-ethyl]-1H-indole: Part B (1.43 g, 3.3 mmol) was dissolved in ethanol (30 mL) and 25% aqueous sodium hydroxide (10 mL) and the resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (30 mL), concentrated in vacuo to remove most of ethanol, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo.

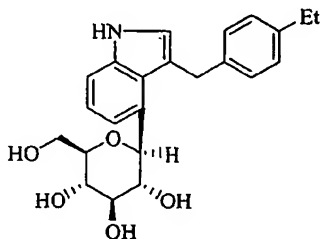
The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (1:4) to provide the title compound (1.0 g, 91%) as a light brown oil.

C. 5-Bromo-1-(tert-butyl-dimethyl-silanyl)-3-[2-(4-methoxy-phenyl)-ethyl]-1H-indole: To a suspension of sodium hydride (0.081 g, 4.0 mmol) in anhydrous THF (2 mL) was added dropwise a solution of Part C (0.85 g, 2.7

- mmol) in anhydrous THF (3 ml) at 0°C. After stirring at 0°C for 30 min, a 1.0 M solution of tert-butyl-chloro-dimethyl-silane in anhydrous THF (3.2 mL, 3.2 mmol) was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred overnight. The reaction was then quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate / hexane (0.5:100) to provide the title compound (0.92 g, 79%) as a light yellow oil.
- 10 D. 5-(β-D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole: The title compound was prepared as a white solid, from Part C by the same procedure as described in Example 1, Part E, F and G. <sup>1</sup>HNMR (300MHz, CD<sub>3</sub>OD) δ 7.58 (s, 1H), 7.31 (d, J = 8.06Hz, 1H), 7.18 (dd, J = 8.39, 1.59Hz, 1H), 7.10 (dd, J = 6.63, 2.16Hz, 2H), 6.92 (s, 1H), 6.81 - 6.78 (m, 2H), 4.21 (d, J = 8.99Hz, 1H), 3.91 - 3.87 (m, 1H), 3.75 (s, 3H), 3.73 - 3.69 (m, 1H), 3.54 - 3.51 (m, 2H), 3.49 - 3.45 (m, 2H), 3.00 - 2.98 (m, 2H), 2.94 - 2.90 (m, 2H). MS: m/z (M+Na) 436.

#### Example 4

##### 3-(4-Ethylbenzyl)-4-(β-D-glucopyranosyl)-1H-indole



20

- A. (4-Bromo-1H-indol-3-yl)-(4-ethyl-phenyl)-methanone: To a suspension of AlCl<sub>3</sub> (3.0 g, 22.5 mmol) in dichloromethane (50 mL) was added a solution of 4-bromoindole (2.21 g, 11.3 mmol) in dichloromethane (25 mL) at room temperature over the period of 20 mins, followed by the addition of a solution of 4-ethyl-benzoyl chloride (2.5 mL, 17 mmol) in dichloromethane (25 mL) over the period of 20 mins. The resulting solution was stirred at room temperature overnight, and saturated sodium bicarbonate solution was added in a water-ice

bath to quench the reaction. The aqueous layer was extracted with dichloromethane. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was triturated in diethyl ether to obtain the title compound (1.8 g, 48%) as white solids.

- 5 B. (1-Benzenesulfonyl-4-bromo-1H-indol-3-yl)-(4-ethyl-phenyl)-methanone: A mixture of a compound prepared from Part A (1.6 g, 5 mmol), tetrabutylammonium bromide (0.16 g, 0.5 mmol) and benzenesulfonyl chloride (1.3 g, 7.5 mmol) in 25% aqueous sodium hydroxide (10 mL) and benzene (50 mL) was stirred at room temperature overnight. The reaction mixture was quenched by addition of water and  
10 extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo and chromatographed on silica gel eluting with ethyl acetate/hexane (30:100) to give the title compound (1.80 g, 76%).

- C. 1-Benzenesulfonyl-4-bromo-3-(4-ethyl-benzyl)-1H-indole: To a  
15 suspended  $\text{AlCl}_3$  (0.8 g, 6 mmol) in dichloromethane (10 mL) was added borane-tert-butylamine complex (0.52 g, 6 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 mins followed by addition of a solution of a compound from Part B (0.94 g, 2 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature overnight, and NaOH (3M, 20  
20 mL) was added with crushed ice to quench the reaction. The basic aqueous layer was extracted with dichloromethane. The organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product (0.90 g, 99%) was pure enough for the next step without further purification.
- 25 D. 4-Bromo-3-(4-ethyl-benzyl)-1H-indole: Part C (0.90 g, 2 mmol) was dissolved in 1:1 mixture of ethanol and THF (20 mL) with 50% aqueous sodium hydroxide (2 mL). The resulting solution was brought to reflux for 3 h. After cooling to room temperature, the mixture was diluted with water (20 mL), concentrated in vacuo to remove most of ethanol, and extracted with ethyl acetate. The organic extracts were  
30 washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with ethyl acetate/hexane (30:100) to give the title compound (0.53 g, 84%) as a colorless oil.

E. 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole: The title compound was prepared as a white solid, from Part D by the same procedure as described in Example 1, Part D, E, F and G.  $^1\text{H}$ NMR (300MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.33 (dd,  $J = 7.42, 1.64$  Hz, 1H), 7.18 (d,  $J = 1.79$  Hz, 1H), 7.16 - 7.07 (m, 5H), 6.90 (s, 1H), 4.72 (d,  $J = 9.64$  Hz, 1H), 4.35 (d,  $J = 16.5$  Hz, 1H), 4.26 (d,  $J = 16.4$ , 1H), 3.69-3.52 (m, 3H), 3.44 - 3.39 (m, 2H), 2.95 (s, 1H), 2.58 (q,  $J = 7.58\text{Hz}$ , 2H), 1.19 (t,  $J = 7.65\text{Hz}$ , 3H). MS:  $m/z$  (M+Na) 420.

## H. Biological Examples:

EXAMPLE 1**Materials and Methods**

5 Cloning of the human SGLT1 and human SGLT2 cDNAs and construction of the mammalian expression vector: The human SGLT1 cDNA (Genbank M24847) was cloned from human small intestine. Human SGLT2 cDNA (Genbank M95549) was cloned from human kidney. Both full cDNAs were  
10 subcloned into pcDNA and sequenced to verify the integrity of the construct.

Generation of CHO-K1 cells stably expressing human SGLT1 or human SGLT2: Transfection of CHO-K1 cells was performed using DMRIE-C reagent (Life Technologies, Gaithersburg, MD). Transfectants were then selected in the  
15 presence of the antibiotic G418 (Gibco-BRL, Grand Island, NY) at 400 µg/ml. Individual clones were then characterized using the functional assay described below.

Cell-based assay for sodium-dependent glucose transport: Cell lines stably  
20 expressing human SGLT1 or SGLT2 were then used for functional analysis of Na<sup>+</sup>-dependent glucose uptake. Briefly, cells were plated at a density of 65,000 cells per well in a 96-well plate and allowed to grow for 48 hours. Cells were subsequently washed one time with Assay Buffer (50 mM HEPES pH 7.4, 20 mM Tris, 5 mM KCl, 1 mM MgCl<sub>2</sub>, 1 mM CaCl<sub>2</sub> and 137 mM NaCl) and  
25 treated with compound in the absence or presence of NaCl for 15 minutes. Cells were then labeled with <sup>14</sup>C -α-methylglucopyranoside (AMG, Sigma, St. Louis, MO) a non-metabolizable glucose analog specific for sodium-dependent glucose transporters as previously described (Peng, H. and Lever J.E. Post-transcriptional regulation of Na<sup>+</sup>/glucose cotransporter (SGLT1) gene  
30 expression in LLC-PK1 cells. J Biol Chem 1995; 270:20536-20542.). After 2 hours the labelled cells were washed three times with ice-cold PBS. After aspiration, cells were solubilized using Microscint 20 (Packard, Meriden, CT) and Na-dependent <sup>14</sup>C-AMG uptake was quantified by measuring radioactivity.



Plates were counted in a TopCount (Packard, Meriden, CT). Results are reported as the % inhibition or IC50 value from a representative experiment. Variability for the functional assay was typically within 20 %.

5 TABLE 3

Example #	CHOK-SGLT2	CHOK-SGLT1
	IC50 (uM)	IC50 (uM)
4	12% Inh at 10 uM	inactive
3	60% Inh at 10 uM	inactive
2	1.395 ± 0.067	inactive
1	0.132 ± 0.024	inactive

EXAMPLE 210 **In Vivo Assay for Efficacy**

Male Zucker Diabetic Fatty (ZDF) rats (7-8 weeks) were obtained from Charles River. Animals were maintained on a 12-hour light/dark cycle in a temperature-controlled room. Animals were given ad libitum access to food (standard  
15 rodent diet Purina 5008) and water. Animals were fasted for 12 hours prior to initiation of the experiment. On the morning of the experiment, animals were administered vehicle (0.5 % methylcellulose) or compound by oral gavage (1ml/kg). After one hour, animals received an oral glucose challenge (4 ml/kg of 50% solution) and were immediately placed in metabolism cages. Animals  
20 were given free access to water and urine was collected for 4 hours. Urinary glucose was quantified using the Trinder Reagent (Sigma).

**EXAMPLE 3****Effects on Plasma Glucose, Plasma Insulin, Plasma Triglycerides, Plasma Free Fatty Acids, Liver Weight, and Body Weight**

5

To examine the effect of an SGLT inhibitor in combination with an RXR agonist, female db/db mice (6-7 weeks of age/Jackson Labs, ME) are treated daily for 11 days with vehicle (0.5% methylcellulose), an RXR agonist (0.1 –10 mpk (mg/kg)), an SGLT inhibitor (100 mpk), or an RXR agonist plus SGLT inhibitor. Mice (n=8 animals/group) receive the test compounds or vehicle by oral gavage in a volume of 10 ml/kg of body weight. Body weight is recorded on day 1, prior to dosing, and days 4, 8 and 11. Eighteen hours after the final dose, mice are weighed and anesthetized with CO<sub>2</sub>/O<sub>2</sub> (70:30). Mice are then bled by retro-orbital sinus puncture into 2 mL heparinized polypropylene tubes on ice. Plasma samples are then assayed for glucose, insulin, triglycerides, and free fatty acids. Livers are excised, weighed and frozen.

The SGLT inhibitors and RXR agonists have distinct mechanisms of action. Improved glycemic control, measured as a decrease in plasma glucose, plasma insulin, plasma free fatty acids, or plasma triglycerides, or a combination thereof, can be observed at lower concentrations of an RXR agonist when given in combination with an SGLT inhibitor. Therefore, a leftward shift in the dose-response curve for effect of an RXR agonist on the above parameters can become apparent. In addition, the weight gain observed following treatment with RXR agonists is less pronounced when given with the SGLT inhibitor, since SGLT inhibitors' promotion of the urinary excretion of glucose and loss of calories from the body is demonstrated by reduction in weight or weight gain. Also, since SGLT inhibitors promote a mild diuresis, the edema (and the edematous weight gain) commonly observed after treatment with RXR agonists can be less pronounced or absent. A reduction in the amount of an RXR agonist such as MX-6054 necessary to achieve efficacy in turn improves the side-effect profile. The decreased side effects can include such conditions as fatty liver, increased liver weight, body weight gain, heart

weight gain, edema, cardiac hypertrophy, hepatohypertrophy, hypoglycemia, and hepatotoxicity, or any combination thereof.

5

#### EXAMPLE 4

**Effects on plasma Glucose, HbA1c, Hematocrit, Plasma Insulin, Plasma Triglycerides, Plasma Free Fatty Acids, Total Cholesterol, HDL, Plasma Drug Levels, Liver Weight, Heart Weight, Fat Content and Body Weight**

10

To examine the effect of an SGLT inhibitor in combination with an RXR agonist, male ZDF rats (6 weeks of age/GMI) are treated daily for 28 days with vehicle (0.5% methylcellulose), an RXR agonist (0.1 mpk-10mpk), SGLT inhibitor (3-100 mpk), or an RXR agonist plus SGLT inhibitor. Rats (n=8  
15 animals/group) receive the test compounds or vehicle by oral gavage in a volume of 2 ml/kg of body weight. Body weight is recorded on day 1, prior to dosing, and twice a week for the duration of the study. On the day prior to the final dose, animals are fasted overnight. One hour after the final dose, rats are weighed and anesthetized with CO<sub>2</sub>/O<sub>2</sub> (70:30). Rats are then bled by retro-  
20 orbital sinus puncture into 2 mL heparinized polypropylene tubes on ice. Rats then receive a glucose challenge (2 g/kg p.o) and are placed in metabolism cages for the urine collection (4 hours). Animals are then sacrificed and epididymal fat pads, livers, and hearts are excised, weighed and frozen for histological examination. Plasma samples are then assayed for glucose,  
25 HbA1c, insulin, hematocrit, plasma drug levels, total cholesterol, HDL, free fatty acids, and triglycerides. Urine volume and urinary glucose, protein, osmolarity, electrolytes (Na, K, Cl), BUN and creatinine are measured.

The SGLT inhibitors and RXR agonists have distinct mechanisms of  
30 action. Improved glycemic control, measured as a decrease in plasma glucose, HbA1c, plasma insulin, or plasma triglycerides, or a combination thereof, can be observed at lower concentrations of RXR agonists when given in combination with an SGLT inhibitor. Therefore, a leftward shift in the dose-

response curve for effect of RXR agonists on the above parameters can become apparent. In addition, the weight gain observed following treatment with RXR agonists is less pronounced when given with the SGLT inhibitor, since SGLT inhibitors' promotion of the urinary excretion of glucose and loss of calories from the body is demonstrated by reduction in weight or weight gain. Also, since SGLT inhibitors promote a mild diuresis, the edema (and the edematous weight gain) commonly observed after treatment with RXR agonists can be less pronounced or absent. This can be demonstrated by a reduction in the RXR agonist-induced increase in heart weight. A reduction in the amount of RXR agonists necessary to achieve efficacy in turn improves the side-effect profile. The decreased side effects can include such conditions as fatty liver, increased liver weight, body weight gain, heart weight gain, edema, cardiac hypertrophy, hepatohypertrophy, hypoglycemia, and hepatotoxicity, or any combination thereof.

15

The above examples can also show that the oral administration of an SGLT inhibitor in combination with an antidiabetic agents, such as an RXR modulator, improve the status of other markers of diabetes mellitus including glycosylated hemoglobin (Hgb A1C) levels. Particularly, the oral administration of an SGLT inhibitor in combination with one or more RXR modulators can reduce body weight or body weight gain as well as liver weight or liver weight gain, compared to administration of one or more RXR modulators alone.

20

Thus, for treating diabetes, particularly Type II diabetes mellitus, or Syndrome X, a compound of Formula (IV) in combination with one or more antidiabetic agents, such as an RXR agonist that increases insulin sensitivity, may be employed comprising administering repeated oral doses of the compound of Formula (IV) in the range of about 25 to 1000 mg once or twice daily and repeated doses of the anti-diabetic agent or agents at jointly effective dosages. The jointly effective dosage for antidiabetic agents disclosed herein may be readily determined by those skilled in the art based on standard dosage guidelines. In particular, such combined administration can be

25

30

effective to accomplish reduction of body weight, body weight gain, liver weight, or liver weight gain in the subject.

5        Additionally, a method comprising (a) administering to a subject a jointly effective amount of a glucose reabsorption inhibitor; and (b) administering to the subject a jointly effective amount of an antidiabetic agent such as an RXR modulator can be used to reduce body weight, body weight gain, or liver weight of the subject in need thereof, wherein the combined administration can be in any order and the combined jointly effective amounts provide the desired  
10    therapeutic effect.

      Also, a method comprising (a) administering to a subject a jointly effective amount of a glucose reabsorption inhibitor; and (b) administering to the subject a jointly effective amount of an antidiabetic agent can be used to  
15    control body weight, body weight gain, liver weight, or liver weight gain of the subject having diabetes, Syndrome X, or associated symptoms or complications, wherein the combined administration can be in any order and the combined jointly effective amounts providing the desired therapeutic effect.

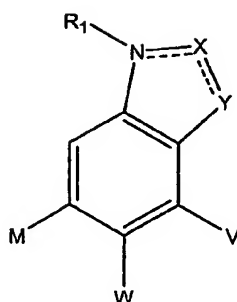
20        Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, time of administration and  
25    concomitant diseases, will result in the need to adjust dosages.

      While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual  
30    variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

What is claimed is:

CLAIMS

- 5      1. A compound of formula IV:

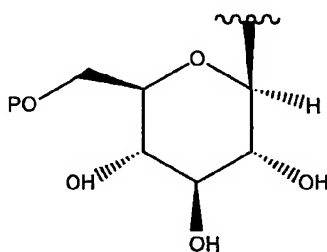


(IV)

wherein:

one of the dashed lines between  $NR_1$  and X or between X and Y is present, or both are absent;

two of V, M, and W are H and the third is



$R_1$  is H, or  $C_{1-4}$  alkyl; or, where the dashed line between  $NR_1$  and X is present,

$R_1$  is absent;

X is N, C=O, CH, or C-Q-Z;

Y is N-Q-Z or C-Q-Z, where X is N, C=O, or CH;

Y is CH, where X is C-Q-Z;

5 Q =  $-(CH_2)_n-$  where n = 1 or 2;

P = H, C<sub>1-7</sub> acyl, or C<sub>1-6</sub> alkoxy carbonyl;

10 Z is substituted or unsubstituted, and is selected from C<sub>3-7</sub> cycloalkyl, phenyl, a 5- or 6- membered heteroaryl having 1 or 2 heteroatoms independently selected from N, O, and S, a biaryl, a 9- or 10-membered fused bicycyl, and a fused heterobicycyl, wherein said fused heterobicycyl has between 1 and 4 heteroatoms independently selected from N, O, and S; or a pharmaceutically acceptable salt, thereof.

15

2. A compound of claim 1, wherein R<sub>1</sub> is H or absent.

3. A compound of claim 1, wherein Z is independently substituted with between 1 and 3 substituents independently selected from C<sub>1-4</sub> alkoxy, phenoxy, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, halo, hydroxy, cyano, amino, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> aminoalkyl, mono and di C<sub>1-4</sub> alkylamino, phenyl, C<sub>1-4</sub> alkylaminosulfonyl (SO<sub>2</sub>NHR), amino(C<sub>1-4</sub> alkylsulfonyl) (NHSO<sub>2</sub>R), di C<sub>1-4</sub> alkylaminosulfinyl (SONHRR), C<sub>1-4</sub> alkylamido (NHCOR), C<sub>1-4</sub> alkylcarbamido (CONHR), 5-6 membered heterocycyl containing between 1 and 3 heteroatoms independently selected from N, S, and O; and wherein the substituent(s) on Z can be further independently substituted with between 1 and 3 substituents independently selected from C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl, halo, hydroxy, cyano, amino, mono or di C<sub>1-4</sub> alkyl amino and C<sub>1-4</sub> alkylthio.

30

4. A compound of claim 1, wherein Z is 4-substituted phenyl, 3,4-disubstituted phenyl, benzhydryl, substituted or unsubstituted thiophenyl, biaryl, benzofuranyl, hydrobenzofuranyl, dihydrobenzofuranyl, 4-substituted pyridyl, ,

benzo[b]thienyl, chromanyl, benzothiophenyl, indanyl, naphthyl, and 2,3-dihydro-benzo[1,4] dioxan.

5. A compound of claim 3, wherein Z is unsubstituted or substituted with  
5 between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl.
6. A compound of claim 1, wherein Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl,  
10 (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl.
7. A compound of claim 1 wherein R<sub>1</sub> is H;
8. A compound of claim 1, wherein n is 1.  
15
9. A compound of claim 8, wherein R<sub>1</sub> is H or absent.
10. A compound of claim 1, wherein Z is biphenyl, 4-(3-pyridyl)phenyl, 4-(2-thienyl)phenyl, 4-(1H-pyrazol-1-yl)-phenyl, (4-ethyl)phenyl, (4-propyl)phenyl),  
20 (4-methoxy)phenyl, dihydrobenzofuran-5-yl, or dihydrobenzofuran-6-yl; and Z is unsubstituted or substituted with between 1 and 2 substituents independently selected from methoxy, ethoxy, fluoro, chloro, methyl, ethyl, propyl, butyl and isopropyl.
- 25 11. A compound of claim 10, wherein n is 1.
12. A compound of claim 10, wherein R is H.
13. A compound of claim 1, wherein M and V are H.  
30
14. A compound of claim 1, wherein M and W are H.
15. A compound of claim 1, wherein X is CH and Y is C-Q-Z.



16. A compound of claim 1, wherein X is C-Q-Z and Y is CH.
17. A compound of claim 15, wherein R<sub>1</sub> is H or absent, and n = 1.
18. A compound of claim 1, selected from examples: 3-(4-Ethylbenzyl)-5-( $\beta$ -D-glucopyranosyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-(4-methoxybenzyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-[2-(4-methoxyphenyl)-ethyl]-1H-indole and 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole.
19. A compound of claim 1, selected from 2-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole; 3-[2-(2,3-Dihydro-benzofuran-5-yl)-ethyl]-5-( $\beta$ -D-glucopyranosyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-(5-methyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzimidazole; 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1,3-dihydro-benzimidazol-2-one and 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzotriazole.
20. A compound of claim 1, selected from 3-(4-Ethylbenzyl)-5-( $\beta$ -D-glucopyranosyl)-1H-indole; 2-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-1H-indole; 5-( $\beta$ -D-Glucopyranosyl)-3-(5-methyl-2-thienyl)-1H-indole; 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzimidazole and 3-(4-Ethylbenzyl)-4-( $\beta$ -D-glucopyranosyl)-3H-benzotriazole.
21. A pharmaceutical composition, comprising a compound of claim 1, 5, 6, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.
22. A pharmaceutical composition of claim 21, comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

23. A method for treating diabetes in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.
- 5 24. A method of claim 23, wherein said diabetes is type II diabetes.
25. A method for lowering serum glucose in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.
- 10 26. A method for treating impaired glucose tolerance in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.
- 15 27. A method for treating or inhibiting impaired glucose tolerance in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.
- 20 28. A method for reducing the body mass index, body weight, or percentage body fat in a mammal, said method comprising administering to a mammal in need of treatment an effective amount of a pharmaceutical composition of claim 21.
- 25 29. A method of claim 28, wherein said reduction of body mass index is a method for treating obesity or an overweight condition.
30. A method for inhibiting the sodium glucose transporter in a cell, by exposing said cell to a compound of claim 1 or a metabolite thereof.
- 30 31. A method for treating diabetes or Syndrome X, or associated symptoms or complications thereof in a subject, comprising

- a) administering to said subject a jointly effective amount of a glucose reabsorption inhibitor of formula (IV); and
- b) administering to said subject a jointly effective amount of a second antidiabetic agent,

5

said co-administration being in any order and the combined jointly effective amounts providing the desired therapeutic effect.

32. The method of claim 31, wherein the second antidiabetic agent is an  
10 RXR agonist.

33. The method of claim 31, wherein the diabetes or Syndrome X, or associated symptoms or complications thereof is selected from IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis,  
15 polycystic ovarian syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts.

34. The method of claim 31 wherein the diabetes or Syndrome X, or associated symptoms or complication thereof is IDDM.

20

35. The method of claim 31, wherein the diabetes or Syndrome X, or associated symptoms or complications thereof is NIDDM.

36. The method of claim 31, wherein the diabetes or Syndrome X, or  
25 associated symptoms or complications thereof is IGT or IFG.

37. The method of claim 31, further comprising administering to said subject a jointly effective amount of a third antidiabetic agent.

30 38. The method of claim 37, wherein the third antidiabetic agent is selected from

(aa) insulins,

- (bb) insulin analogues;
- (cc) insulin secretion modulators, and
- (dd) insulin secretagogues.

5     39.    The method of claim 31, wherein the glucose reabsorption inhibitor is an SGLT inhibitor.

40.    The method of claim 31, wherein the glucose reabsorption inhibitor is an SGLT1 inhibitor.

10

41.    The method of claim 31, wherein the glucose reabsorption inhibitor is an SGLT2 inhibitor.

42.    The method of claim 31, wherein the glucose reabsorption inhibitor is a  
15    compound of Formula (IV) or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof.

43.    The method of claim 31, wherein the jointly effective amount of an SGLT  
20    inhibitor is from about 10 to 1000 mg.

44.    The method of claim 31, wherein the jointly effective amount of an SGLT inhibitor is an amount sufficient to reduce the plasma glucose excursion following a meal.

25

45.    A method for inhibiting the onset of diabetes or Syndrome X, or associated symptoms or complications thereof in a subject, said method comprising

- 30    (a) administering to said subject a jointly effective amount of a glucose reabsorption inhibitor of formula (IV); and
- (b) administering to said subject a jointly effective amount of a second antidiabetic agent,

said co-administration being in any order and the combined jointly effective amounts providing the desired prophylactic effect.

5    46.    The method of claim 45, wherein said onset is from pre-diabetic state to NIDDM.

47.    A pharmaceutical composition comprising a glucose reabsorption inhibitor of formula (IV), a second antidiabetic agent, and a pharmaceutically  
10    acceptable carrier.

48.    The pharmaceutical composition of claim 45, 46, or 47, wherein the glucose reabsorption inhibitor is an SGLT inhibitor.

15    49.    The pharmaceutical composition of claim 45, wherein the glucose reabsorption inhibitor is an SGLT1 inhibitor.

50.    The pharmaceutical composition of claim 45, wherein the glucose reabsorption inhibitor is an SGLT2 inhibitor.  
20

51.    A process for formulating a pharmaceutical composition, comprising formulating together a glucose reabsorption inhibitor, a second antidiabetic agent, and a pharmaceutically acceptable carrier.

25    52.    A process for making a pharmaceutical composition comprising mixing one or more glucose reabsorption inhibitors in combination with a second antidiabetic agent for the preparation of a medicament for treating a condition selected from IDDM, NIDDM, IGT, IFG, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovarian syndrome, hypertension,  
30    ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataracts.

53. A method for inhibiting the progression of a prediabetic condition in a subject to a diabetic condition, comprising

- 5 (a) administering to said subject a jointly effective amount of a glucose reabsorption inhibitor of formula (IV); and  
(b) administering to said subject a jointly effective amount of an second diabetic agent,

10 said co-administration being in any order and the combined jointly effective amounts providing the desired inhibiting effect.

54. The method of claim 53 wherein said condition is IGT or IFG.

15 55. The method of claim 53 wherein said inhibiting of the progression of a prediabetic condition is prevention of the progression of the prediabetic condition to a diabetic condition.

20 56. The method of claim 53, wherein the glucose reabsorption inhibitor is a compound of formula (IV), optionally having one or more hydroxyl or diol protecting groups, or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture, ester, prodrug form, or a pharmaceutically acceptable salt thereof.

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